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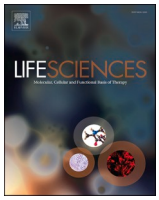

Review article

The role of vasoactive intestinal peptide in pulmonary diseases

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ABSTRACT

Vasoactive intestinal peptide (VIP) is an abundant neurotransmitter in the lungs and other organs. Its discovery dates back to 1970. And VIP gains attention again due to the potential application in COVID-19 after a research wave in the 1980s and 1990s. The diverse biological impacts of VIP extend beyond its usage in COVID-19 treatment, encompassing its involvement in various pulmonary and systemic disorders. This review centers on the function of VIP in various lung diseases, such as pulmonary arterial hypertension, chronic obstructive pulmonary disease, asthma, cystic fibrosis, acute lung injury/acute respiratory distress syndrome, pulmonary fibrosis, and lung tumors. This review also outlines two main limitations of VIP as a potential medication and gathers information on extended-release formulations and VIP analogues.

Background

According to a thorough examination conducted for the Global Burden of Disease Study 2017, lung cancer and chronic obstructive pulmonary disease (COPD) are the primary reasons for mortality worldwide [1]. COVID-19 and the subsequent acute lung injury/acute respiratory distress syndrome (ALI/ARDS), which poses a severe threat to public health globally, have also attracted much attention [2]. In recent years, studies have been conducted on various pulmonary diseases, including pulmonary arterial hypertension (PAH), asthma, and pulmonary fibrosis (PF). Vasoactive intestinal peptide (VIP) is a non-adrenergic and non-cholinergic neurotransmitter, exerting a significant regulatory function in the pathophysiological mechanisms associated with the onset and progression of diverse pulmonary diseases. This review summarizes relevant studies concerning VIP and possible links to various pulmonary diseases.

1. Introduction

VIP is a 28-amino acid peptide processed from a 170-amino acid precursor [3]. It belongs to the secretin/glucagon family [4], including pituitary adenylate cyclase-activating polypeptide (PACAP). During the early 1970s, VIP was initially extracted and defined from the duodenum of pigs [5]. As an inhibitory non-adrenergic and non-cholinergic neuropeptide, VIP has initially been considered a gastrointestinal hormone regulating the physiological activity of the digestive system. With more in-depth insight, it has been accepted that VIP plays an indispensable role in regulating body homeostasis as an essential neurotransmitter. VIP is extensively found in cholinergic presynaptic neurons of the central nervous system and peripheral peptidergic neurons that innervate

Abbreviations: 5-HT, 5-hydroxytryptamine; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic guanosine monophosphate; CI, cardiac index; COPD, chronic obstructive pulmonary disease; CREB, cAMP response element binding protein; CSE, cigarette smoke extract; DAG, diacylglycerol; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; ET, Endothelin; GRF, growth hormone-releasing factor; HBEC, human bronchial epithelial cells; HIF, hypoxia-inducible factor; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; IP_3, 1,4,5-triphosphate inositol; IPA, intrapulmonary artery; IPF, idiopathic pulmonary fibrosis; KO, knock-out; LPS, lipopolysaccharide; MAPK, Mitogen-activated protein kinase; MCT, monocrotaline; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; NFATc3, NFAT isoform c3; NF-κB, nuclear factor kappa-B; NLRP3, the NACHT, LRR, and PYD domains-containing protein 3; NO, nitric oxide; NSCLC, non-small-cell lung cancer; PACAP, pituitary adenylate cyclase-activating polypeptide; PAH, pulmonary arterial hypertension; PDE, Phosphodiesterase; PF, pulmonary fibrosis; PHT, precapillary pulmonary hypertension; PIP2, phosphatidylinositol biphosphate; PKA, protein kinase A; PKC, protein kinase C; PVR, pulmonary vascular resistance; ROS, reactive oxygen species; RVSP, right ventricular systolic pressure; SCLC, small-cell lung cancer; SREBP, sterol regulatory element-binding protein; TNF-α, tumor necrosis factor α; TREM, Triggering receptors expressed on myeloid cells; VEGF, vascular endothelial cell growth factor; VIP, Vasoactive intestinal peptide; VPAC, VIP pituitary adenylate cyclase-activating polypeptide; WT, wild-type; α-AN, α-alumina nanoparticle; α-SMA, α-smooth muscle actin.

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various tissues, including the lung and heart [6].

The biological activities of VIP are mainly mediated by two type II G-protein-coupled receptors: VIP pituitary adenylate cyclase-activating polypeptide 1 (VPAC1) and VPAC2. Besides, VIP can also bind with low affinity to the PACAP receptor [7]. VIP binding sites have been identified in numerous tissues. In the respiratory system, high densities of VPAC1 and VPAC2 are found in large airway smooth muscle, submucosal glands, airway epithelium, and alveolar walls [8]. After the injection of purified ^{123}I-VIP into patients with intestinal adenocarcinomas or endocrine tumors, the lung is the primary site of ^{123}I-VIP uptake, indicating the massive distribution of VIP reception in lung tissue in some pathological conditions [9].

Upon binding to VIP receptors, VIP is capable of initiating a sequence of signaling pathways (Fig. 1). The major signaling pathway is as follows. Initially, the VIP binds with either VPAC1 or VPAC2. Then, it engages with Gs proteins to produce significant quantities of cyclic adenosine monophosphate (cAMP) by degrading adenosine triphosphate (ATP) *via* adenylyl cyclase. cAMP converts inactive protein kinase A (PKA) into active PKA, phosphorylates proteins in organisms, and produces various biological effects [8]. For example, phosphorylation of cAMP response element binding protein (CREB) promotes nuclear translocation of CREB, thereby altering gene expression [10]. Furthermore, VIP has the ability to function *via* the phosphatidylinositol signaling pathway. In this signal transduction pathway, when the membrane receptor binds to VIP, the Gq protein on the membrane is activated. Then the Gq protein activates phospholipase Cβ, which converts phosphatidylinositol biphosphate (PIP2) into two intracellular secondary messengers: diacylglycerol (DAG) and 1,4,5-triphosphate inositol (IP_3). IP_3 mobilizes the endoplasmic reticulum calcium store to release Ca^{2+} into the cytoplasm and participate in a series of reactions. DAG triggers the activation of protein kinase C (PKC) in the presence of Ca^{2+}, leading to a series of downstream reactions through PKC to execute the cellular response [8,10]. Additionally, VIP may exert respiratory effects mediated by nitric oxide (NO). VIP enhances NO synthase activity and raises the NO levels in respiratory cells [8]. Also, VIP participates in the mammalian target of rapamycin (mTOR) signaling pathway. The expression of mTOR and its phosphorylation at S6 is enhanced by VIP, while the mRNA and protein expression of mTOR is reduced by VIP silencing. Inhibition of mTOR signaling with rapamycin reduces the expression of endogenous VIP and VIP-induced S6

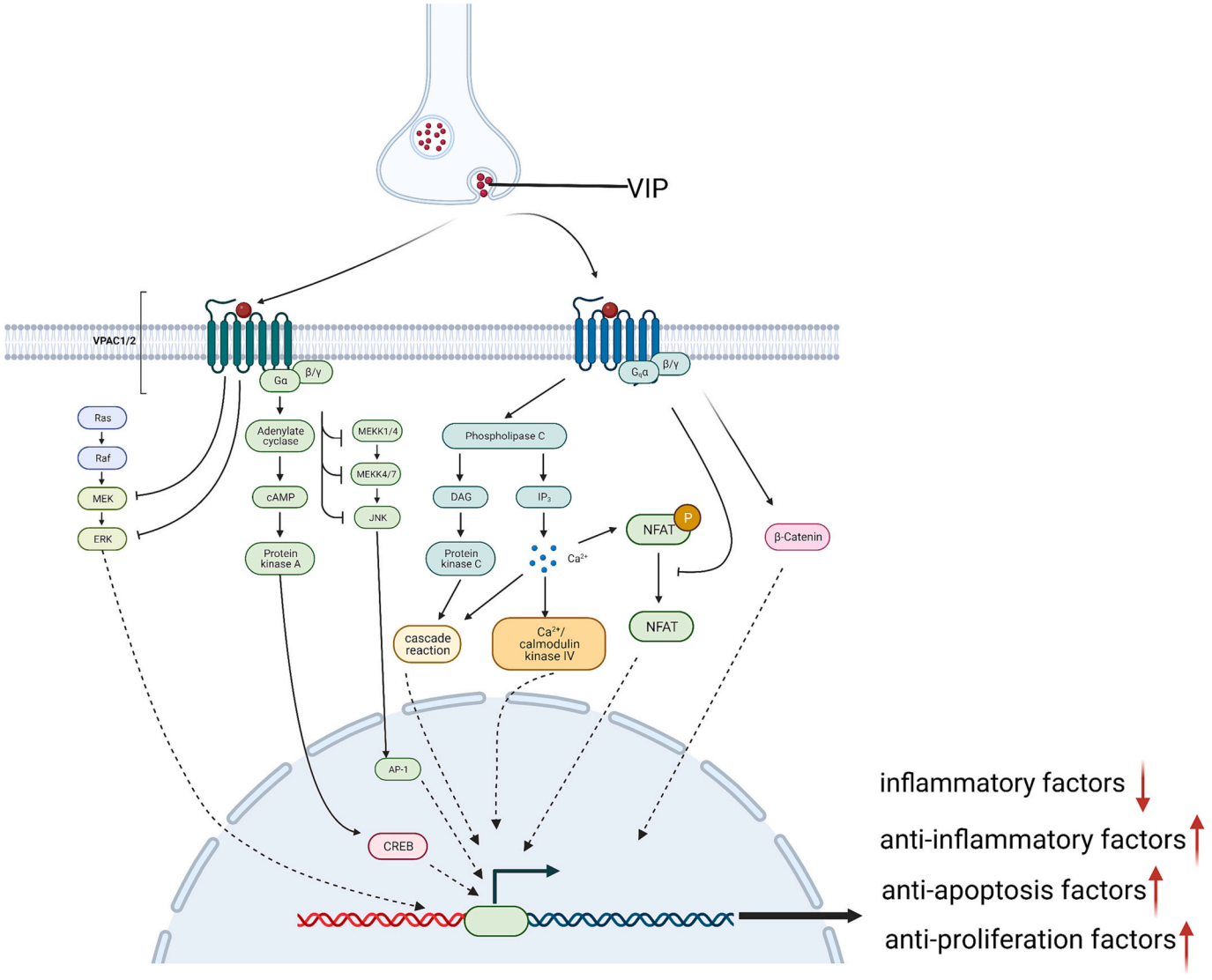

Fig. 1. VIP-related signaling pathway. VIP regulates various signaling pathways *in vivo* by activating G protein-coupled receptors VPAC1 and VPAC2 on the cell membrane. These pathways include the PKA, PKC, NFAT, and ERK signaling pathways. By modulating these pathways, VIP regulates the expression of relevant genes, leading to downstream physiological and pathological changes.
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phosphorylation [11]. VIP inhibits airway smooth muscle cell proliferation in a mouse model of asthma *via* the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway [12]. VIP inhibits the MEKK1/MEK4/JNK signaling pathway in endotoxin-activated microglia [13]. VIP stimulates osteogenesis differentiation of bone marrow-mesenchymal stem cells by activating the Wnt/β-Catenin signaling pathway [14]. The mitogen-activated protein kinase (MAPK) signaling pathway is also involved in the signaling transduction of VIP [15].

2. Biological effects of VIP

2.1. Anti-inflammation

Inflammation is a defense reaction of the body in response to stimuli, and its basic pathological features are alteration, exudation, and proliferation. In the development of several lung diseases, such as PAH, COPD, ARDS, and PF, inflammation plays a crucial role. A train of studies has demonstrated that VIP possesses anti-inflammatory capabilities (Fig. 2, Table 1). VIP treatment decreases inflammation, perivascular cell infiltrates, and inflammatory cytokines in bronchoalveolar lavage fluid of PAH mice [16]. VIP emerges as an endogenous modulator of inflammation, partly by suppressing the nuclear factor of activated T cells (NFAT) activation. NFAT is a family of transcription factors that serve as dominant regulators of allergic pulmonary inflammation. NFAT signaling is facilitated by calcineurin, a Ca^{2+}-dependent phosphatase. Upon dephosphorylation, NFAT is relocated from the cytoplasm to the nucleus, where it becomes activated and binds with the transcription factor AP-1 to facilitate the expression of inflammation-related genes, thus playing a role in the progression of inflammation [16]. Inhibition of NFAT activation is the mechanism by which VIP suppresses inflammation. Furthermore, it has been reported that VIP regulates the expression of various cytokines. VIP suppresses the synthesis of tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), IL-12, and NO, while promoting the production of IL-10 and IL-1 receptor antagonist (IL-1Ra). Effects on TNF-α, IL-10, IL-12, and NO are mainly mediated through VPAC1 receptors [17]. The regulation of inflammation is contingent upon the equilibrium between local pro-inflammatory and anti-inflammatory factors. Pro-inflammatory factors such as TNF-α, IL-6, IL-12, and NO are frequently encountered, whereas anti-inflammatory factors such as IL-10 and IL-1Ra are also present. VIP can suppress the generation of pro-inflammatory cytokines and promote the expression of anti-inflammatory cytokines. Meanwhile, VIP significantly reduces the expression of the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3), the most well-characterized inflammasome sensor molecule in lung tissue [18]. Due to this property, VIP can also be defined as a natural anti-inflammatory factor. *In vitro*, VIP can inhibit TNF-α production from lipopolysaccharide (LPS)-stimulated RAW246.7 cells in a dose- and time-dependent manner, proving the protective role of VIP [19]. Studies indicate that the absence of the VIP gene in mice results in airway inflammation that can be partially remedied by VIP therapy [20]. Evidence also shows that inhalable powder formulation of VIP derivative attenuates neutrophilic airway inflammation in cigarette smoke-exposed rats [21]. The presented evidence serves to further demonstrate the anti-inflammatory properties of VIP.

2.2. Bronchodilation

VIP functions as a bronchodilator, inducing relaxation in isolated strips of human bronchus and lung parenchyma *in vitro* (Fig. 2, Table 1). The basal tone and relaxant effect of VIP is significantly enhanced by the pretreatment of this tissue with indomethacin. VIP relaxes the isolated human bronchial smooth muscle *in vitro*, and its efficacy is >50 times stronger than isopropanol [22]. It is the most potent bronchodilator discovered so far [23]. The synthetic VIP analogue Ro 25-1553 is a selective VPAC2 receptor agonist that causes a bronchodilation effect in guinea pigs *in vivo*. The maximal bronchodilation effect of inhaled Ro

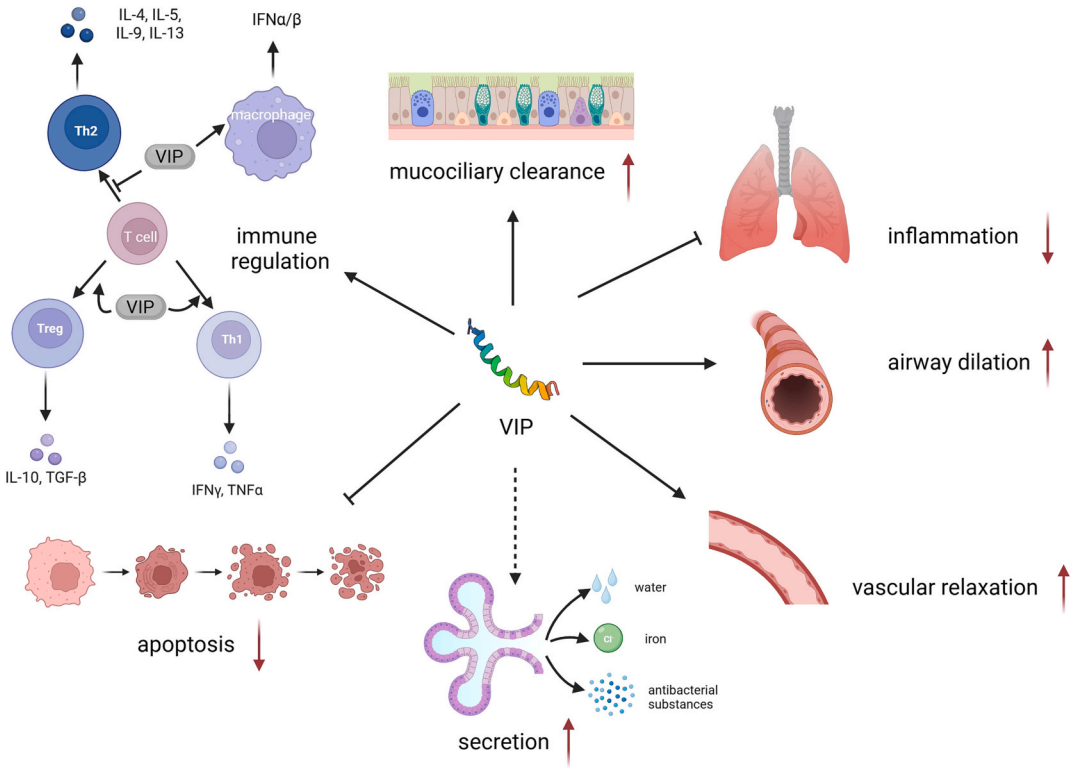

Fig. 2. Biological effects of VIP. VIP exerts various biological effects in the body, including anti-inflammation, bronchial dilation, vascular relaxation, secretion regulation, apoptosis inhibition, immunity regulation, and promotion of mucosal clearance, *etc.*
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Table 1
A summary table of the biological roles of VIP.

Effects	Biological roles of VIP
Anti-inflammation	• Reducing inflammatory cell infiltration • Inhibiting the synthesis of pro-inflammatory factors, such as IL-6 and TNF-α • Promoting the production of anti-inflammatory factors, such as IL-10 and IL-1Ra • Inhibiting the activation of the transcription factor NFAT to regulate the expression of inflammation-related genes • Reducing the expression of NLRP3 inflammasome • VIP gene-deficient mice develop spontaneous airway inflammation
Bronchodilation	• Inducing relaxation of isolated human bronchial, lung parenchyma, and bronchial smooth muscle • Leading to bronchodilation effect in guinea pigs *in vivo* • Owning similar effects to the bronchodilator formoterol • VIP analogues have a longer duration of action and better relaxation
Vascular relaxation	• Inducing relaxation in pulmonary blood vessels, coronary arteries, IPA, and other arteries • Relaxing vascular smooth muscle • VIP-induced vasodilation is less prominent in the bronchial circulation than in the trachea
Glandular secretion regulation	• Regulating secretion of antibacterial substances in submucosal glands • Regulating mucus secretion • Stimulating Cl^- and HCO_3^- secretion
Immune regulation	• Exhibiting immunomodulatory effects in particular immune organs and peripheral lymphoid tissues • Suppressing the production of pro-inflammatory chemicals from innate immune cells • Restraining differentiation of T cells into the Th1 subset while promoting Treg and Th2 differentiation • Maintaining immune homeostasis in early pregnancy • Playing an antiviral role by regulating alveolar macrophages to increase IFN-α/β production
Anti-apoptosis effect	• Obstructing caspase activation • Boosting the expression of the antiapoptotic Bcl-2 • Reducing apoptosis caused by TNF-α, Fas ligand, and angiogenin II • Lung cancer cells can be made more susceptible to apoptosis by treatment with a VIP receptor antagonist
Other	• Modulating the oxidant/antioxidant balance • Beneficial effects on mucociliary clearance • Maintaining alveolar integrity

25-1553 at 600 μg was similar to that of the reference bronchodilator formoterol within 24 h. Notably, the bronchodilator effect attenuated after 5 h of the Ro 25-1553 inhalation, while the bronchodilator effect of formoterol persisted until inhalation after 12 h [24]. Derived from RO 25-1553 through chemical modification, RO5024118 is a selective VPAC2 receptor agonist that demonstrates superior stability of neutrophil elastase when compared to its parent compound. In isolated human and guinea pig airways, RO5024118 induced bronchodilation comparable to RO 25-1553 and the long-acting beta-agonist salmeterol and more potent than the native VIP and the short-acting beta-agonist salbutamol. In 5-hydroxytryptamine (5-HT)-induced bronchoconstriction in guinea pigs, RO5024118 exhibited similar inhibitory activity to RO 25-1553 and lasted longer [25].

2.3. Vascular relaxation

VIP was characterized as a vasodilatory peptide initially [26]. It positively impacts pathological conditions of the heart and lungs by inducing relaxation in pulmonary blood vessels and coronary arteries. This, in turn, mitigates the risk of cardiopulmonary diseases, such as pulmonary hypertension and myocardial ischemia [7]. According to a study, VIP was found to cause relaxation in the intrapulmonary artery (IPA) isolated from cat lungs in a concentration-dependent manner. Additionally, the study suggests that local enzymatic degradation may not be the primary route for the inactivation of VIP in the isolated IPA [27]. A comparative study done in 1993 investigated the pharmacological properties of the PACAPs and VIP, including the ability to relax vascular smooth muscle *in vitro*. The study found that VIP and PACAP-27 were similarly potent in relaxing rat mesenteric arteries, porcine coronary arteries, and rat gastric smooth muscle, whereas PACAP-38 was either more or less potent than the other two peptides depending on the tissue model [28]. VIP-induced vasodilation is more prominent in the trachea than in the bronchial circulation. VIP has been suggested as a potential therapy for primary pulmonary hypertension due to its potent vasodilatory properties [8] (Fig. 2, Table 1). A comprehensive explanation of this will be provided in a subsequent section of the review.

2.4. Glandular secretion

VIP-containing nerve fibers and nerve endings innervate the submucosal glands of the human pulmonary airways [29]. The submucosal glands secrete a range of antibacterial substances such as lysozyme, lactoferrin, collectins, and defensins, in addition to fluid and mucin [30]. Disordered mucus secretion displays a severe problem with upper and lower respiratory tract diseases. *VPAC2* mRNA has also been identified in human submucosal glands [31]. Based on the evidence, it can be inferred that VIP regulates mucus secretion. However, the effects of VIP on mucus secretion seem controversial because different studies lead to opposite results sometimes. In *ex vivo* ferret tracheas, VIP could promote mucus secretion from submucosal glands [32]. Also, in ferret and rat tracheal glands, VIP stimulates secretion. Whereas cholinergic secretion is demonstrated to be inhibited by VIP in the ferret trachea [8]. In the human airway submucosal gland, VIP evokes the increase of cAMP, thus stimulating Cl^- and HCO_3^- secretion [33]. In the human trachea, VIP inhibits the methacholine-stimulated release of glycoproteins and lysozyme due to the increased formation of cAMP [8] (Fig. 2, Table 1). However, it is still possible that VIP impacts mucus secretion through alternative signaling pathways. In light of the contentious results, further research involving human tissues and cell lines must be carried out to determine the pathways of VIP signal transduction that stimulate or inhibit airway secretion, particularly in secretory-related illnesses like COPD and cystic fibrosis.

2.5. Immune regulation

VIP, a significant endogenous immunoregulatory neuropeptide, is crucial in establishing and sustaining immune deviation (Fig. 2, Table 1). VIP is widely distributed in the nervous system and is synthesized not only by neurons but also by immune cells, which express VIP receptors [34]. VIP exhibits immunomodulatory effects in particular immune organs and peripheral lymphoid tissues where VIP dominates or immune cells are present. VIP emerges as a regulator that suppresses the production of pro-inflammatory chemicals from innate immune cells and restrains differentiation of T cells into the Th1 subset while promoting Treg differentiation and activity [34]. VIP generated by T cells has also been shown to promote the development of Th2 and inhibit Th1 differentiation [35]. The Th2/Th1 ratio increases, with VPAC2 playing a more significant role in immune responses than VPAC1. The inhibitory effects of VIP on Th17 are observed *in vivo* but not *in vitro* [34]. Recent research shows VIP may offer protection against intestinal mucosal immune dysfunction caused by certain bacteria [36]. VIP synthesized by extravillous trophoblast cells is involved in maintaining immune homeostasis in early pregnancy [37]. After the respiratory syncytial virus infection, VIP can play an antiviral role by regulating alveolar macrophages to increase IFN-α/β production [38]. In summary, VIP is a vital factor that regulates the immune system.

2.6. Anti-apoptosis effect

There is an increasing volume of evidence indicating that VIP can

control cell death *via* apoptosis (Fig. 2, Table 1). According to certain studies, VIP has been shown to decrease lung injury by obstructing caspase activation and boosting the expression of the antiapoptotic Bcl-2, both of which impede cell apoptosis [39,40]. Apoptosis has been induced in primary cultures of rat AECs and human cell line A549 by TNF-α, Fas ligand, and angiogenin II. VIP has shown dose-dependent inhibition of apoptosis in these experimental models [15]. VIP promotes cell survival immensely *via* the activation of PKA and MAPK. PKA and MAPK trigger the activation of CREB through phosphorylation, subsequently leading to the upregulation of Bcl-2. Given its ability to hinder apoptosis through various pathways and mechanisms, VIP is likely to act as a physiological regulator of programmed cell death [15]. The protection of rat alveolar L2 cells from cigarette smoke-induced apoptosis is possible through VIP derivatives, as per studies [41]. Meanwhile, lung cancer cells can be made more susceptible to apoptosis caused by chemotherapeutic agents with a synthetic VIP receptor antagonist [42].

2.7. Other effects

VIP appears to contribute to modulating the oxidant/antioxidant balance at the gene and protein levels. According to a proteomics study, the VIP knock-out (KO) mice have significantly higher levels of a new antioxidant protein, lung carbonyl reductase 3. Additionally, the RT-PCR results indicate that carbonyl reductase 3 is also elevated in these mice [43]. Furthermore, VIP has been shown to improve lung damage caused by oxidative stress [44].

The beneficial effects of VIP on mucociliary clearance have been reported in studies. It was noted that a concentration of 0.1 μM of VIP was able to increase mucociliary clearance velocities to a significant extent. However, this effect was found to be less potent than the equivalent doses of carbachol and isoproterenol in *ex vivo* tracheas from adult ferrets [32].

VIP plays a regulatory function in maintaining alveolar integrity by controlling pulmonary surfactant, a complex blend of lipids and proteins produced by ATII cells. Pulmonary surfactant plays a crucial role in the regulation of host defense and inflammation in the lungs. VIP enhances the synthesis of pulmonary surfactant phospholipid and elevates pulmonary surfactant protein A expression in ATII cells [44]. VIP also increases the synthesis of phosphatidylcholine, the major component of pulmonary surfactant, by enhancing choline-phosphate cytidylyltransferase activity [45]. VIP enhances wound healing and proliferation of human bronchial epithelial cells (HBEC) suffered from mechanical damage. The recovery of the wound area by HBEC is accelerated in the presence of VIP. The regulation of the healing process involves the PKA, PKC, Calmodulin, ERK, and CREB pathways, which can be impeded by using a VPAC1 receptor antagonist. VIP also increased the expression of E-cadherin mRNA and protein in HBEC, suggesting that the protective effects of VIP on wound healing may be related to its ability to increase the expression of E-cadherin [46–48].

3. Role of VIP in pulmonary diseases

3.1. Role of VIP in PAH

PAH is characterized by elevated pulmonary arterial pressure with pulmonary vascular proliferation and remodeling, which can eventually lead to right heart failure [3]. PAH is defined by a mean pulmonary artery pressure exceeding 25 mmHg. Despite its high mortality rate, the precise pathophysiology of this chronic lung disease remains unclear. Nevertheless, mounting evidence indicates that inflammation plays a crucial role in its development [49]. Over the last 25 years, significant advancements have been made in drug development for PAH, creating a range of medications to treat this condition [50]. Epoprostenol was the initial drug to be studied for enhancing symptoms and providing a survival benefit [51]. Despite its effectiveness, the medication also presents notable adverse reactions, including but not limited to headaches, nausea, and diarrhea [52,53]. Antagonizing endothelin (ET) receptors is also one of the existing therapeutic strategies. ET-1, an important endogenous vasoconstrictor, binds to the ET receptors ET-A and ET-B on the pulmonary artery intima to enhance vascular tone [54]. ET receptor antagonists, such as bosentan, have been shown to improve pulmonary hemodynamics, symptoms, and exercise capacity (6-minute walk distance) [53,55]. Phosphodiesterase (PDE) inhibitors are also considered effective solutions for symptomatic relief by reducing the degradation of cAMP and cyclic guanosine monophosphate (cGMP), thereby increasing their levels [56,57]. These methods induce vasorelaxation and inhibition of the proliferation of smooth muscle cells in the pulmonary artery [53]. Regrettably, while the abovementioned remedies may alleviate symptoms, they do not address the underlying issue at its core. As the ailment worsens and drug resistance arises, individuals are focusing on the creation of promising novel medications.

The promising future of VIP in treating PAH is suggested by its biological effects, which include the relaxation of blood vessels, improvement of cardiopulmonary blood circulation, and anti-inflammatory properties [7,16,22,23,58]. Multiple studies have been done on animal models. Deleting the VIP gene leads to spontaneous moderately severe PAH in mice during air breathing [59]. While there is no specific mouse model for PAH, the examination of VIP gene-deficient mice can aid in the investigation of the molecular mechanism of PAH. Also, people use monocrotaline (MCT) to produce a PAH model. After injection of MCT in Sprague Dawley rats, PAH developed, manifested by pulmonary vascular remodeling, lung inflammation, right ventricular hypertrophy, and death. Treating with VIP completely prevents and significantly reverses MCT-induced PAH [58]. Concurrently, VIP down-regulates the expression of ET receptors. Combining VIP and bosentan may result in an additive or synergistic effect [58]. The induction of sustained precapillary pulmonary hypertension (PHT) models in rats through an aorta-caval shunt surgery can give rise to bronchial hyper-reactivity, and VIP has been identified as a potential preventive measure for PHT development [60]. In cases of PAH induced by over-circulation, the pulmonary vascular resistance (PVR) is found to double. The expression of VPAC1 gene is positively correlated with PVR, while the expression of the VIP gene is decreased, indicating that PAH is accompanied by a down-regulation of VIP signaling [61]. Similar results are observed in the MCT-induced PAH model. Decreased VIP expression is associated with the upregulation of VPAC1 and VPAC2. Intravenous injection of selective VPAC2 agonist BAY 55–9837 and VIP improves the cardiac index (CI). They also effectively decrease right ventricular systolic pressure (RVSP) and total pulmonary systolic pressure in MCT-induced PAH [62]. The transfer of the VIP gene *via* adenovirus has been found to inhibit the proliferation of smooth muscle cells in the rat's aortic and pulmonary arteries. When treated with the PKA inhibitor Rp-8-BrcAMPs, the cells' proliferation recovered to about 80 % of the control, while treatment with the PKG inhibitor Rp-8-brcGMP had no significant effect. These results suggest that the antiproliferative action of VIP involves the PKA pathway [63]. The antiproliferative role of VIP is mediated by VPAC1 and VPAC2. VIP 6-28, an antagonist of both receptors, results in significant restoration of proliferation, and VPAC2 appears to play a more dominant role [64]. Patients with PAH have been found to experience changes in VIP, which have been documented. Specifically, it has been observed that the pulmonary VIP serum level in PAH patients is lower than that of healthy [65]. According to a clinical trial conducted on patients, the inhalation of a 100 μg-dose of vasodilating VIP has been found to be advantageous for individuals suffering from PAH. This inhalation can selectively relax pulmonary vessels, enhance stroke volume, and temporarily facilitate venous oxygen saturation in patients [66]. More than one study has reported that VIP decreased the mean pulmonary artery pressure, increased cardiac output, and mixed venous oxygen saturation [67]. The researchers aim to determine if mutations in the human VIP gene can lead to PAH by investigating the correlation between VIP gene mutations and the

development of IPAH. Gene alterations have been detected in the coding region of the VIP gene through direct sequencing in patients suffering from idiopathic PAH. However, there seems to be no correlation between the frequency of alteration in the coding region of the VIP gene and the onset of the disease. So apart from VIP gene, the genetic and environmental modifiers might contribute to the development and persistence of the disease [68]. In general, there is a clear relationship between VIP and PAH. VIP serves as an innovative pharmaceutical agent for managing PAH (Fig. 3).

3.2. Role of VIP in COPD

COPD is a cluster of respiratory ailments marked by a gradual and irreversible airflow constriction, frequently accompanied by emphysema [7]. Cigarette smoke has been considered the leading cause of COPD due to a series of substances contained in it. The mechanism of cigarette smoke links with oxidative stress, an essential mediator of cell death *via* apoptosis or necrosis. The presence of free radicals in tar constituents can lead to cellular penetration, DNA binding, and consequential damage [69]. Cigarette smoke extract (CSE) triggers apoptotic cell death by elevating caspase-3 and matrix metalloproteinase (MMP) activities, which can be mitigated by specific inhibitors, as reported in a study [70]. In comparison to COPD mice, those treated with VIP exhibited a reduction in levels of malondialdehyde (oxidant)/superoxide dismutase (antioxidant), hydroxyproline (a crucial indicator of collagen fiber deposition in the lung), transforming growth factor-β (a primary fibrotic factor), and several pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6). However, when TNF-α and IL-1β could significantly decrease after treating with VIP, the IL-6 decreasing level was not significant [71].

VIP has been thought to be effective for the clinical treatment of COPD (Fig. 4). The cytotoxicity of CSE is caused by the activation of caspase-3 and MMP, which is mitigated by VIP through its binding to the VPAC2 receptor. Protection of VIP against CSE-induced cytotoxicity is partly due to the inhibition of the activation of caspase-3 and MMP [70]. So, VIP could be beneficial in the treatment of COPD. When VIP is conjugated with α alumina nanoparticle (α-AN) to prevent enzyme degradation of VIP, the benefit effects of VIP are even more pronounced. Inhalation of stabilized VIP derivative respirable powder leads to attenuation of plasma eosinophil peroxidase, myeloperoxidase, and lactate dehydrogenase activities, which could be regarded as some inflammation biomarkers. Inhalation of VIP derivative respirable powder also reduces the recruitment of macrophages and granulocytes [72]. VIP also inhibits the recruitment of other inflammatory cells like mast cells [73].

Several studies *in vivo* and *in vitro* have been conducted on patients. At the time of acute exacerbation in COPD, there is a noteworthy increase in serum VIP levels compared to stable COPD. This outcome presents novel possibilities for diagnosing COPD, as VIP may be utilized to identify exacerbation in COPD [74]. Alveolar macrophages are one of the players in the pathogenesis of COPD and contribute to the severity and progression of the disease. Alveolar macrophages from COPD patients present a higher VPAC1 expression, which exceeds VPAC2. Similarly, VPAC1 rises in LPS-activated monocyte-derived macrophages. So, the up-regulation of VPAC1 in macrophages is a mechanism that response to pro-inflammatory stimuli [4]. An increased number of VPAC1, but not VPAC2, is found in the bronchial epithelium, bronchial glands, and vessels of patients with chronic bronchitis. Smokers with chronic bronchitis symptoms also increase the number of VPAC1- and VPAC2-positive monocytes in the bronchial submucosa [75]. The selective VPAC2 receptor agonist RO 25-1553 caused a dose-dependent relaxation of airway and pulmonary artery preparations, with an EC50 of approximately 10 nM and maximal relaxation of 70 %–75 % of the tone [76]. VIP and NFAT isoform c3 (NFATc3) expression correlate in lung tissue from COPD patients and lung NFATc3 activation is associated with disease severity. As previously stated, VIP can hinder the nuclear translocation of NFAT. The expression of VIP may serve as a protective compensatory mechanism [77]. The decreased VIP concentration can lead to airway inflammation and hyperresponsiveness [73].

3.3. Role of VIP in asthma

Asthma is a complex, persistent, and inflammatory disease characterized by airway hyperresponsiveness [7]. Wheezing, coughing, chest

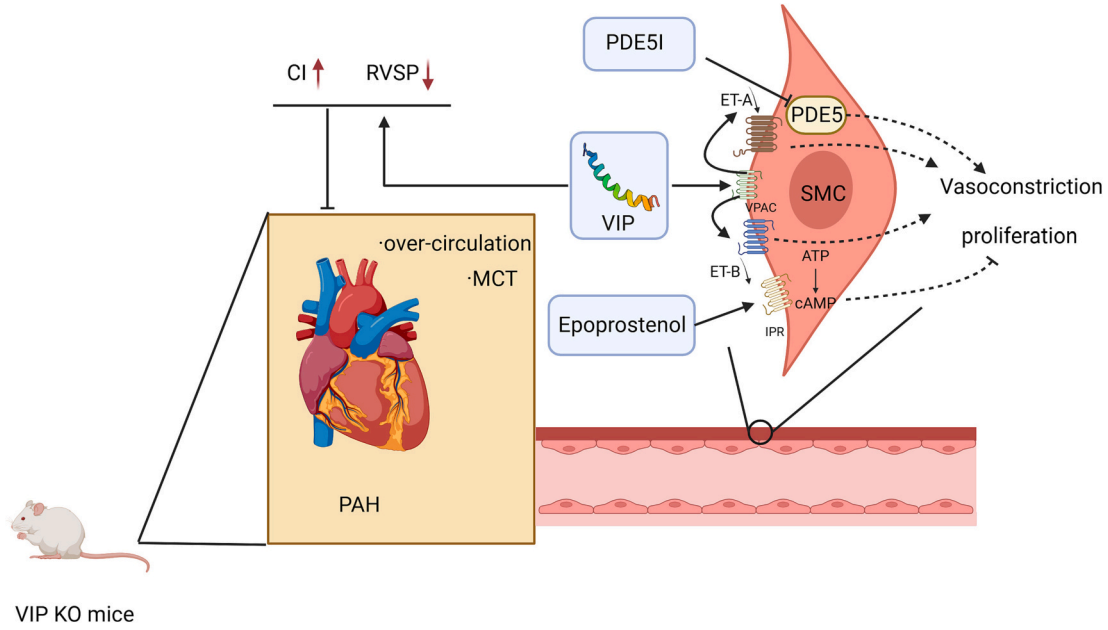

Fig. 3. Role of VIP in PAH. PAH can occur spontaneously in VIP knockout mice, while animal models can also be induced with pulmonary hypertension through circulatory overload and MCT. ET receptor blockers, PDE5 inhibitors, and prostaglandin I_2 agonists have been used to treat pulmonary hypertension. VIP also has the potential to be utilized as a medication for addressing PAH. VIP can inhibit the contraction and proliferation of vascular smooth muscle by down-regulating the expression of ET-A and ET-B receptors while increasing CI and reducing RVSP to relieve PAH. Administration of VIP to mice completely prevents and reverses PAH. (Created with biorender.com)

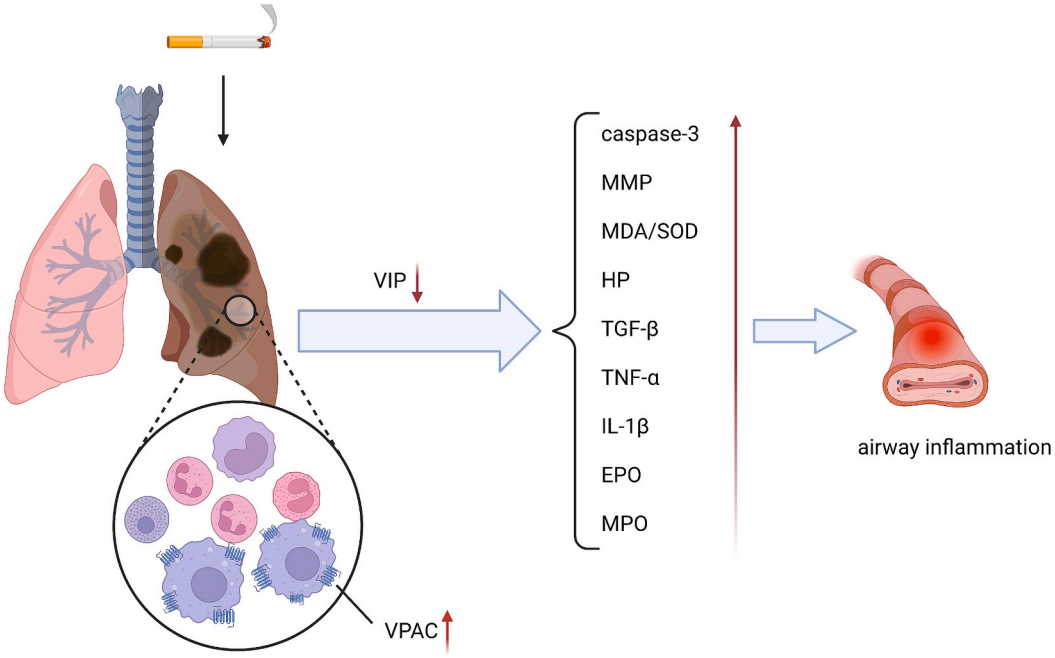

Fig. 4. Role of VIP in COPD. Cigarettes are one of the leading risk factors for COPD. CSE is often used to model COPD in mice. In COPD lungs, there was a reduction in the expression of VIP, while there was an increase in the expression of various pro-apoptotic, pro-inflammatory, and pro-fibrotic factors. Nevertheless, the addition of VIP was successful in counteracting this transformation. The expression of VPAC receptors on the surface of inflammatory cells in COPD lung, such as macrophages and monocytes, is upregulated, and the expression of VPAC1 receptors is mainly upregulated.
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tightness, and difficulty breathing are among the clinical manifestations. As a non-communicable disease, asthma affects around 334 million people worldwide. Although the etiology of asthma remains incompletely understood, the most prevalent risk factors are genetic susceptibility and environmental factors such as certain allergens [78].

Both asthma and COPD share similarities in their pathogenesis and therapeutic drugs, leading to previous studies that have examined the impact of VIP on both conditions simultaneously (Fig. 5). The activation of NFAT is a contributing factor in the development of asthma. The absence of the VIP gene results in the activation of the NFAT pathway, and it is likely that VIP functions as a natural inhibitor of this pathway [79]. Lots of inflammatory responses are thought to be mediated by T-helper type2 lymphocytes (Th2 cells). Eosinophils, neutrophils, mesenchymal cells, and mast cells are also involved in inflammatory events [70]. In ovalbumin-treated Balb/c mice, α-AN-VIP significantly reduced the number of eosinophils, Th2 cytokines, serum IgE level, and airway hyperresponsiveness [80]. *Aspergillus fumigatus* antigen is utilized to create allergic asthma models in mice. The sensitization of C57BL/6 wild-type (WT) and VPAC2 KO mice with the antigen results in a significant increase in *MUC5AC* mRNA and sustained high levels of serum IgE in VPAC2 KO mice as compared to WT mice, indicating that VPAC2 KO mice exhibit more severe symptoms [81]. This research suggests the absence of VPAC2 fails to protect mice from asthma. This indicates that the VPAC2 receptor plays a vital role in protecting against asthma, but the role of VPAC1 cannot be ruled out. VIP KO mice exhibited airway hyperresponsiveness and peribronchial airway inflammation, increased production of pro-inflammatory factors IL-5, IL-6, and IFN-γ, accompanied by accumulation of lymphocytes and eosinophils [43]. Airway remodeling, a critical factor in asthma development, is linked to the activity of airway smooth muscle cells. VIP has been found to hinder the phosphorylation of the ERK1/2 signaling pathway and the expression of Cav-1 on the surface of smooth muscle cells, which plays a role in the cell cycle and signal transduction pathway. This, in turn, reduces the proportion of S-phase cells in the cell cycle and inhibits the proliferation of airway smooth muscle cells [12].

Accordingly, it has been observed that the immune activity of VIP is non-existent in individuals with asthma, which implies that VIP deficiency could cause airway hyperresponsiveness, ultimately resulting in asthma [82]. In a clinical trial, an intravenous injection of VIP (6 pmol/kg/min) is given to two groups of patients with stable asthma. It was found that VIP significantly increased the peak expiratory flow rate, though the effect was weaker than that of the bronchodilator albuterol [83]. In another trial, intravenous infusion of VIP at a rate of 6 pmol/kg/min relieves histamine-induced bronchoconstriction and improves asthma symptoms [84]. It is worth mentioning that when VIP was administered at a dose of 50–200 μg by atomization inhalation, the patient did not show significant improvement in lung function. However, an increase in FEV1 was observed in all experimental subjects by intravenous injection [85]. In a separate study, 25 adult asthmatic patients were examined, and their VIP plasma levels were observed to be lower than those of normal individuals. This finding highlights the importance of VIP in the development of asthma [73].

3.4. Role of VIP in cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a single gene and results in multisystemic disease, particularly affecting the lungs. The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes an epithelial ion channel responsible for transporting chloride and bicarbonate [86]. This results in abnormal mucus hydration and clearance. Classical CF is characterized by chronic pulmonary infection and inflammation [87]. The mainstream management strategies are augmenting mucociliary clearance and treating infections actively [88]. Restoration of damaged CFTR function by small molecule therapy has also gained attention. Numerous alternative methods are being investigated in clinical trial pipelines to enhance survival rates and minimize adverse effects [89].

The significance of VIP in CF is receiving more attention (Fig. 6), with research indicating the absence of VIP secretion in airway glands

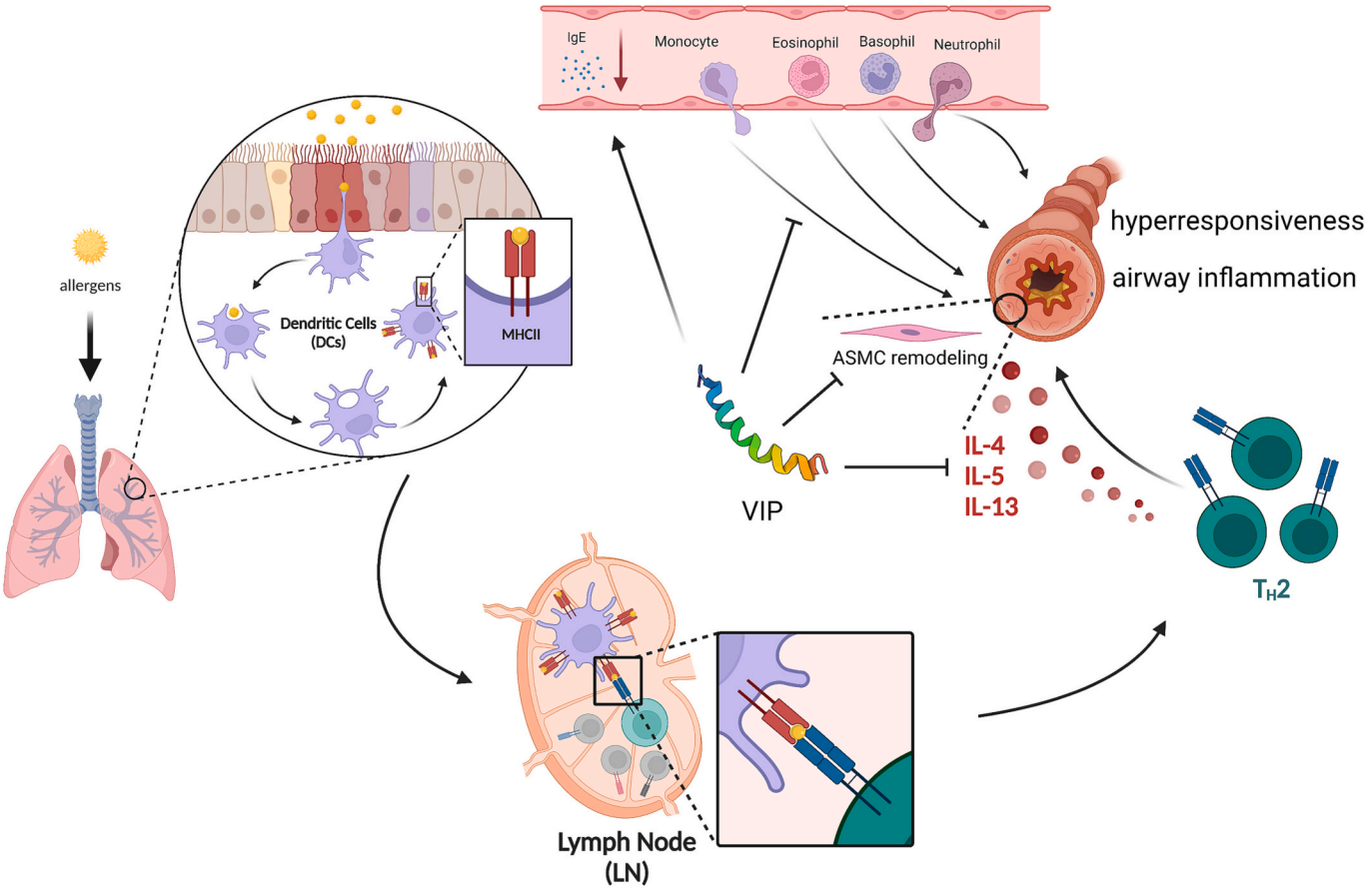

Fig. 5. Role of VIP in asthma. Dendritic cells take up, process, and present antigens to activate T cells and polarize them toward Th2 cells. Subsequently, Th2 cells secrete cytokines like IL-4 and IL-5, which facilitate the development of asthma. A range of inflammatory cells, including eosinophils, also play a role in the development of asthma. Elevated serum IgE levels may trigger the degranulation of mast cells and basophils, leading to the release of histamine and exacerbating asthma. VIP has the ability to hinder the discharge of Th2 cytokines, obstruct the movement of inflammatory cells like granulocytes and monocytes, diminish the concentration of serum IgE, and impede the alteration of airway smooth muscle cells, thereby restraining asthma.
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affected by the condition [90]. Prior research has indicated that CF patients may experience a loss of the ample neuronal networks responsible for VIP secretion surrounding glands [91]. The regulation of CFTR-dependent secretion is influenced by VIP. One study has previously disclosed that VIP triggers the stimulation of the VPAC1 receptor and PKC signaling cascade and enhances CFTR stability and insertion at the apical membrane of airway epithelial cells by reducing its internalization rate [92]. VIP increases CFTR aggregation into cholesterol-dependent clusters and reduces the lateral mobility of CFTR within and between membrane microdomains [93]. Moreover, the addition of VIP corrects the defects of gene mutation of F508del. In VIP KO mice, the absence of VIP results in CFTR intracellular retention and a subsequent loss of CFTR-dependent chloride current [94]. VIP exposure is essential in maintaining normal and functional CFTR chloride channels. In normal human glands, VIP and ACh produced significant mucus secretion *via* synergistic effects. However, synergy is lost in the glands of CF patients. CF glands fail to secrete mucus in response to VIP [95].

3.5. Role of VIP in ALI/ARDS

ALI and ARDS are life-threatening lung diseases with high mortality. ARDS is frequently linked with acute inflammation and is considered a more severe manifestation of ALI. Although significant breakthroughs have been made due to the continuous exploration of ALI/ARDS, there is still no effective drug that can cure it. The emergence of COVID-19 and the global pandemic have put the therapy of ALI/ARDS in great demand, which might also be helpful for the treatment of COVID-19 [96].

Recently, the significance of VIP in ALI/ARDS has been receiving more attention (Fig. 7). IL-17A is a pro-inflammatory cytokine that recruits neutrophils and interacts with other pro-inflammatory mediators to enhance inflammatory responses. There is a significant increase of IL-17A in bronchoalveolar lavage fluid and lung tissue of mice with ALI. Knockout of IL-17 attenuates lung inflammation induced by LPS [97]. We have reported that VIP decreases LPS-mediated IL-17A expression in a time- and concentration-dependent manner. This process might be mediated *via* the PKA and PKC pathways [98]. The attenuation of LPS-induced ALI in mice is facilitated by VIP expression mediated by lentivirus. The administration of Lenti-VIP results in an increase in respiratory rate, tidal volume, and lung compliance. At the molecular level, Lenti-VIP downregulates TNF-α expression while upregulating IL-10 expression [99]. Additionally, we have reported that VIP inhibits the expression of triggering receptors expressed on myeloid cells-1 (TREM-1) [100], which play a role in the initiation and amplification of ALI. TREM-1 and TREM-2 regulate immune responses to LPS. The mRNA expression of TREM-1 increases in the lungs of mice with ALI, while the mRNA expression of TREM-2 decreases. VIP inhibits the expression of TREM-1 and promotes the expression of TREM-2 in a time- and dose-dependent manner. So, VIP re-balances TREM-1/TREM-2 ratio in ALI [100]. Excessive fibroblast activation during the fibroproliferative phase plays a focal role in the prognosis of ARDS. In ALI mice, the gene expression of col3a1 and hydroxyproline contents increases significantly in lung tissue. However, VIP can reduce the hydroxyproline content and

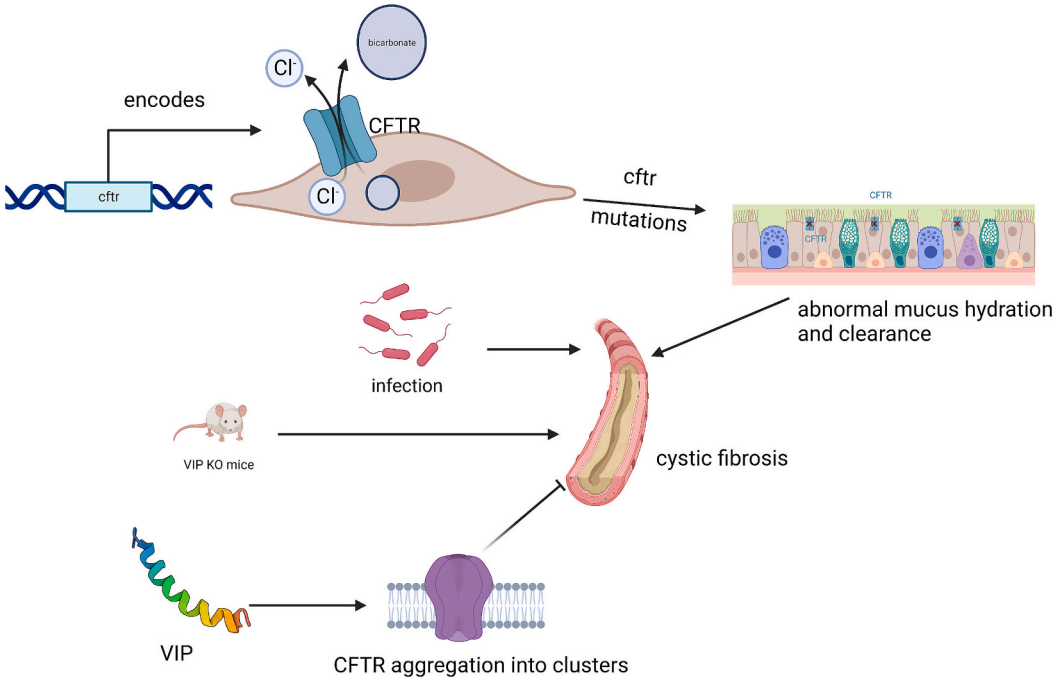

Fig. 6. Role of VIP in cystic fibrosis. Cystic fibrosis is a disease caused by abnormal function of the CFTR channel caused by a single gene mutation. VIP has the ability to enhance CFTR stability, facilitate its insertion onto the apical membrane of airway epithelial cells, encourage CFTR clustering, and decrease its lateral migration between membranes.
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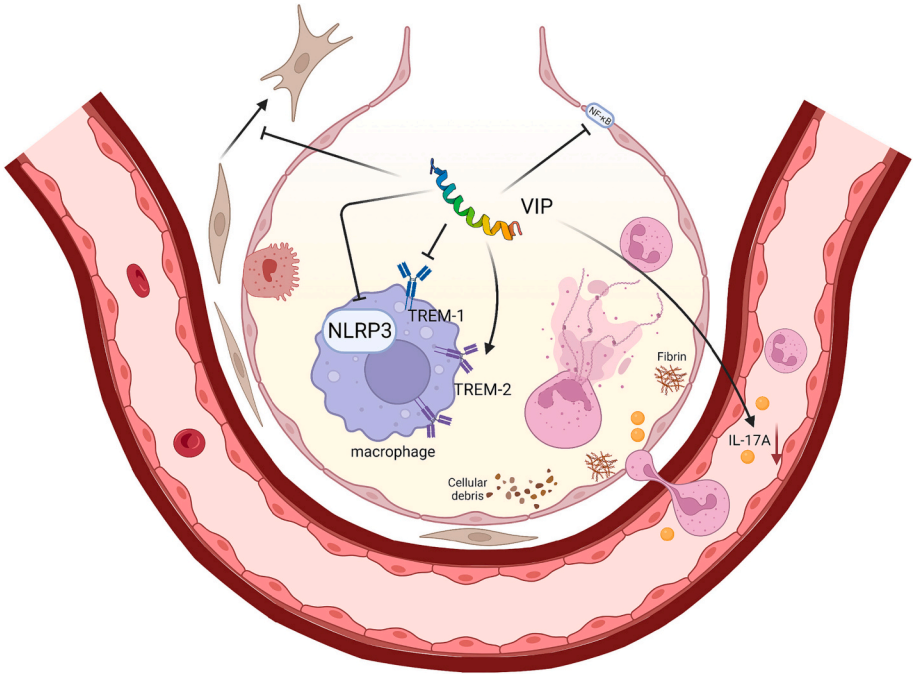

Fig. 7. Role of VIP in ARDS. The essence of ARDS is the pulmonary inflammatory response mediated by various inflammatory cells and their released inflammatory mediators. VIP can reduce the chemotaxis of neutrophils by reducing the expression of IL-17A, inhibit the activation of macrophage NLRP3 inflammasome, deplete the expression of TREM-1, promote the expression of TREM-2 on the surface of macrophages, hinder the differentiation of fibroblasts into myofibroblasts, directly inhibit the activation of NF-κB in alveolar epithelial cells, reduce the release of downstream inflammatory factors, and slow down lung inflammation, thus inhibit ALI/ARDS.
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col3a1 mRNA induced by LPS in NIH3T3 cells by down-regulating the IL-17 receptor [101]. According to a study, estrogens have been found to protect against lung injury beyond their conventional function as a class of female sex hormones. Estradiol, known to offer lung protection, has been observed to stimulate *VIP* mRNA expression in rat lungs rapidly and remarkably. Therefore, the protective effects of estradiol could be

partially attributed to VIP [102].

VIP inhibits the activation of NLRP3 inflammasome in LPS-treated mice and macrophages. NLRP3 is the most well-characterized inflammasome sensor molecule, and the formation of the NLRP3-ASC-caspase-1 complex is necessary for LPS-induced ALI. LPS fails to induce ALI in *Nlrp3*$^{-/-}$ or *caspase-1*$^{-/-}$ mice [103]. Our *in vitro* study has demonstrated that VIP can reduce the expression of NLRP3 inflammasome components and inhibit the formation of the NLRP3 complex [18]. A recent study has revealed that patients with severe COVID-19 exhibit increased VIP levels. *In vitro*, VIP decreases the SARS-CoV-2 RNA content in human monocytes and viral production in lung epithelial cells by preventing SARS-CoV-2-induced activation of transcription factors involved in inflammation and lipid metabolism, including nuclear factor kappa-B (NF-κB) and sterol regulatory element-binding protein 1 (SREBP1) and SREBP2 [104]. Meanwhile, VIP promotes CREB activation, which plays a role in antiapoptotic [15]. Thus, VIP is beneficial in reducing cell death. Aviptadil, a combination of VIP and phentolamine, has been approved by the FDA for treating ARDS related to Covid-19 [105]. Notably, several clinical studies have been conducted to investigate the therapeutic efficacy of Aviptadil. A multicenter, placebo-controlled, double-blinded, randomized trial with 132 adult patients hospitalized for COVID-19 and at high risk for ARDS found that inhaled 67 μg Aviptadil could prevent ARDS in COVID-19 [106]. Another multicenter, placebo-controlled trial, concluding 196 patients with COVID-19 respiratory failure, shows a significant improvement in respiratory distress ratio, reduced IL-6 on Day 3, and increased likelihood of survival at day 60 in critical COVID-19 across all sites of care [107].

3.6. Role of VIP in pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is the predominant form of idiopathic interstitial pneumonia, characterized by chronic, progressive, and fibrotic lung disease, featuring modified extracellular matrix and collagen deposition. IPF has risen over time, and in Asia, it is estimated to range from 0.5 to 4.2 cases per 100,000 individuals per year. The median survival time from diagnosis of IPF is 2–4 years [108]. The progression of PF is attributed to the epithelial-mesenchymal transition, damage of epithelial cells, and excessive activation of fibroblasts, which destroys the alveolar architecture in patients with IPF [109]. The gradual advancement of IPF eventually causes a decline in lung compliance, interference with gas exchange, and, ultimately, respiratory failure, leading to death. Patients typically present with non-specific symptoms of exertional dyspnea. Nintedanib and pirfenidone are approved for the treatment of IPF [108]. Activation of NFATc3 also correlates with the severity of IPF patients. There is a significant positive correlation between NFATc3 mRNA expression and VIP RNA expression only in the lungs of IPF patients. VIP inhibits the nuclear translocation of NFAT, and its elevation exists as a compensatory protective mechanism [77]. According to a recent study of us, VIP has the potential to alleviate murine PF induced by bleomycin. Overexpression of VIP can mitigate lung tissue damage, decrease extracellular matrix deposition, and suppress α-smooth muscle actin (α-SMA) expression. VIP acts against epithelial-mesenchymal transition (EMT) by restoring autophagy in alveolar epithelial cells, alleviating BLM-induced PF [110]. In addition to inhibiting the EMT, VIP obstructed the activation of fibroblasts *via* the downregulation of IL-17RC on fibroblasts [101] (Fig. 8).

3.7. Role of VIP in lung cancer

Lung cancer is one of the most frequent cancers, with an estimated 2 million new cases and 1.76 million deaths annually. Lung cancers are divided into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), subdivided into squamous and non-squamous in histology. The act of smoking is a significant factor in the development of lung cancer. Extensive studies have been conducted on biomarkers such as EGFR mutations and ALK rearrangements in relation to this disease. With a deeper comprehension of the underlying pathogenesis and molecular targets on the cellular surface, a multitude of medications have been produced over the last two decades to combat lung cancer. Bevacizumab, platinum combined with pemetrexed, gefitinib, ceritinib, Pembrolizumab, and numerous other drugs are sanctioned by the FDA. Accelerating drug development and early medication improves patient survival rate and prolongs patient survival time. However, many agents are not affordable in most parts of the world, particularly in developing

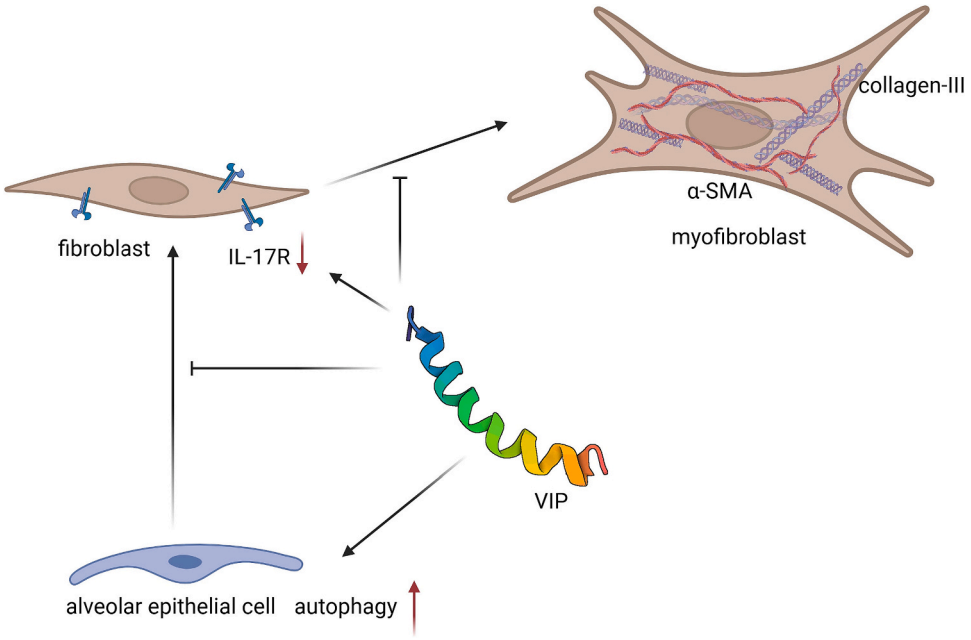

Fig. 8. Role of VIP in pulmonary fibrosis. VIP reduces the expression of IL-17R on the surface of fibroblasts, inhibits the differentiation of fibroblasts into myofibroblasts, and reduces the deposition of collagen and α-SMA. At the same time, VIP can inhibit the transdifferentiation of alveolar epithelial cells into fibroblasts and promote autophagy of alveolar epithelial cells.
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countries. The cost of drugs has become a headache problem for a vast number of individuals [111]. VIP-immunoreactivity has been observed in several types of tumors, including lung cancer. VIP receptors are present in approximately 60 % of lung carcinoma cells.

Furthermore, research has shown that VPAC1 is over-expressed in these tumors, while VPAC2 has not been studied extensively in this context [3]. VIP receptors are also present in 58 % of lung cancer biopsy specimens examined in one study. VIP elevates the secretion of bombesin-like peptides and neurotensin, leading to increased SCLC proliferation [10]. Paradoxically, a study done in 1998 shows VIP inhibits SCLC *in vivo* and *in vitro* through a cAMP-dependent mechanism [112]. Results in the study indicate that VPAC1 is functional *in vitro* and *in vivo*. In most cases, VIP promotes the growth of the tumor. VIP causes increased vascular endothelial cell growth factor (VEGF) mRNA expression in a time- and dose-dependent manner in NSCLC cell line NCI-H157 [113]. The addition of VIP to cancer cells activates the cAMP signaling cascade, which increases the expression of the c-myc gene and c-fos gene, leading to proliferation [10,114]. The disorderly proliferation of cells consumes a large amount of oxygen, creating a hypoxic zone and activating hypoxia-inducible factors (HIFs) responsible for neovascularization and tumor metastasis. HIFs are complexes formed by the cytoplasmic subunit HIF-α and nuclear subunit HIF-β. HIF-α (including HIF-1α, HIF-2α, and HIF-3α) is degraded by the ubiquitin-proteosome system and translocates in the nucleus. Fragments of HIF-α can form heterodimers with HIF-β and bind to hypoxia response elements to induce the expression of various genes, including VEGF, which are directly tumor growth and vascularization. According to a meta-analysis, there is a significant increase in the expression of HIF-1α in lung cancer tissue compared to normal tissue. Additionally, positive HIF-1α expression is associated with lower survival rates among patients diagnosed with NSCLC. The laboratory results indicate that VIP significantly diminishes HIF-1α and HIF-2α in both A549 lung adenocarcinoma cells and human normal bronchial epithelial BEAS-2B cells. The expression pattern of HIF-3α is linked to the cell phenotype, with lower levels observed in A549 cells and higher levels in BEAS-2B cells. The restoration of HIF to its baseline levels in lung adenocarcinoma cells through VIP treatment suggests that the role of VIP may vary depending on the pathophysiological conditions and the specific lung cells or tissues involved [115]. A lipophilic VIP analogue named stearyl-Nle17-neuroten-sin6-11VIP7–28 (SNH) also inhibits lung cancer proliferation. The antiproliferative effect of SNH and the chemotherapeutic agent is at least addictive and synergistic. The advantages of SNH lie in the elevated response rate and reduction in dose and side effects [116]. Immune checkpoint inhibitors are a common treatment for cancer, but they can lead to pneumonia in 10 % to 20 % of patients [117]. Fortunately, inhaled VIP topical therapy has shown promise in reducing alveolitis in individuals with immune checkpoint inhibitor pneumonia [118].

Injection of 0.4 mg/kg of VIPhybrid, a VIP antagonist, reduces tumor growth in nude mice to 69 % [119]. Similarly, an injection of 10 mg/d of VIPhybrid inhibits tumor growth in nude mice by approximately 80 % [120]. VIPhybrid inhibits the increase in VEGF mRNA and cAMP caused by VIP [113]. Another study shows that synthetic VIP receptor antagonists also inhibit tumor proliferation. The use of the antagonists potentiates the chemotherapeutic agents' ability to cause apoptosis of lung cancer cells [42]. The VPAC1 receptor has been identified as a viable option for the targeted delivery of drugs to cancerous cells [119]. VPAC1 can even be utilized to image cancer tumors because VPAC1 density is higher than normal adjacent tissues in mammalian animals like rats and mice [10]. In humans, VPAC imaging can be used to locate tumors that express VPAC because they can intake radiolabeled VIP [121] (Fig. 9).

4. Application limitations of VIP and development of its analogues

The clinical application of VIP is limited due to two main reasons. Firstly, VIP has poor metabolic stabilization. It has an extremely short plasma half-life period. It is estimated that the half-life of VIP is only 1 min [122,123]. VIP is degraded quickly by enzymes such as neutral endopeptidase, mast cell chymase, and mast cell tryptase, which leads to a lack of pharmacological effects [8]. Secondly, there are some obstacles in administration routes. For example, when using traditional intravenous administration, the drug is difficult to target the lungs and may cause side effects in the cardiovascular system [124]. What's more, it is easily degraded in blood. If VIP is administered orally, serious problems will be poor oral availability due to gastrointestinal peptidases, high intestinal and hepatic first-pass metabolism, and limited penetration to the desired site of action [70]. For pulmonary diseases, airway drug delivery is more common, which has the advantage of maximizing drug

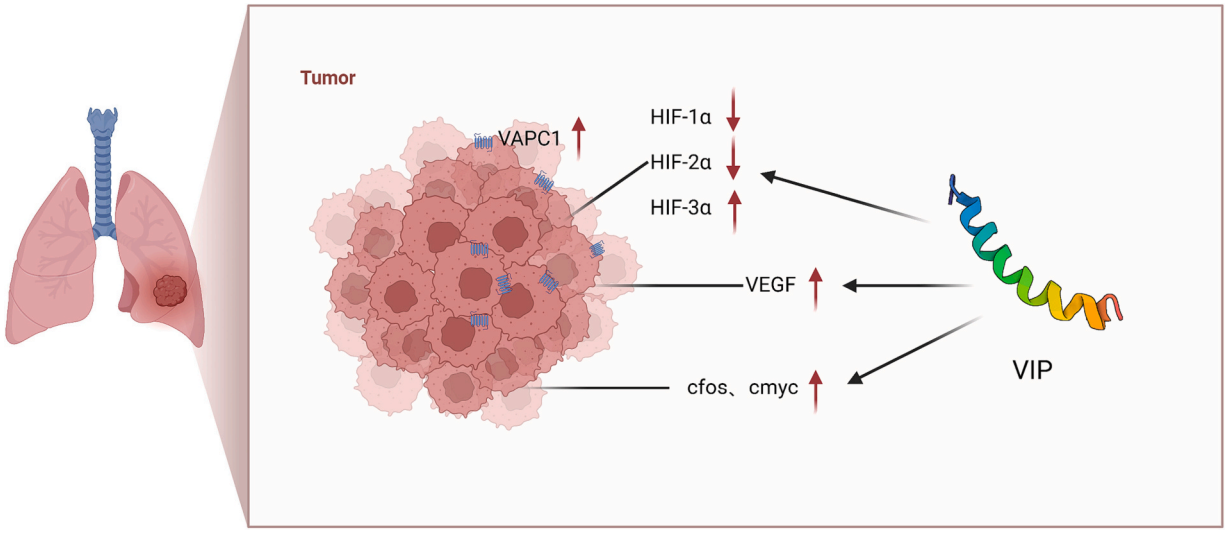

Fig. 9. Role of VIP in lung cancer. VPAC is present in 60 % of lung cancer cells. The expression of VPAC1 is notably augmented in lung cancer cells, and it is the VIP receptor that predominantly contributes to the pathogenesis of lung cancer. The potential application of this characteristic is in the field of tumor imaging. The function of VIP in tumors is a subject of debate, with most research indicating that VIP can stimulate the proliferation of lung cancer cells. The mechanism includes promoting the expression of VEGF, increasing the expression of proto-oncogenes such as c-fos and c-myc, and regulating the expression of HIFs. VIP receptor antagonists were employed to inhibit the growth of lung cancer cells *in vitro* and to suppress the proliferation of xenograft tumor xenografts in nude mice.
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concentration in target organs and reducing systemic side effects [125]. For example, in the treatment of asthma, glucocorticoids and β2 receptor agonists are often used for aerosol inhalation [78]. For VIP, inhaling dry powder preparations can alleviate the difficulty of drug administration to a certain extent. On the one hand, VIP with dry powder as the carrier has high stability during storage, and it can be easily administered as long as its formulation is slightly modified. On the other hand, administration in the form of dry powder inhalation avoids the binding of VIP to VPAC receptors widely distributed in various systems in the body, reducing the risk of side effects [126].

Consequently, a range of VIP analogues have been formulated, and the administration route of VIP has been exhaustively investigated (Table 2). VIP analogues, namely VPAC receptor agonists, can be broadly categorized into VPAC1 selective agonists, VPAC2 selective agonists, and non-selective VPAC agonists. [Ala11, 22, 28]-VIP is regarded as the first highly selective human VPAC1 receptor agonist. People use Ala to replace amino acid residues on VIP molecules one by one, and results show that substitution of Thr11 and Asn28 by alanine reduces affinity for binding to VPAC2 receptor; substitution of Tyr22 by alanine increases EC50 for stimulating adenylyl cyclase activity through interaction with the VPAC2 receptor. Taken together, by combining 3 mutations, [Ala11, 22, 28]-VIP was found [127]. Following this line of thought, several selective VPAC1 receptor agonists have been discovered. Other VPAC1 receptor selective agonists include [K15, R16, L27]-VIP(1-7)/GRF(8-27) [128,129], [D-Ala2, Aib8,18, A9,15,16,22,24-26, Gab27]-hGRF(1-27) (GRF-6) [130], [R16]-chicken Secretin [128,129], [Tyr(9),Dip(18)]VIP(6-23) [131], [Ala(2,8,9,11,19,22,24,25,27,28)]-VIP, [Ala(2,8,9,11,19,24-28)]-VIP [132], [Leu22]VIP [133]. A selective antagonist is also available: PG97-269 [134]. It is worth mentioning that the selective VPAC1 receptor does not only bind to the VPAC1 receptor but has a much higher affinity for the VPAC1 receptor than the VPAC2 receptor, which makes its effect on the VPAC2 receptor negligible. Similarly, selective VPAC2 agonists with high affinity for VPAC2 but low affinity for VPAC1 include acetyl-[E8, K12,27,28,Nle17, A19, D25, L26, G29,30, T31]-VIP(cyclo 21-25) (Ro 25-1553 [76,135]), Ro 25-1392 [136], RO5024118 [25], Ro 24-9981 [137], BAY(Q9Q28C32) PEG43 [138], LBT-3627 [139] and so on. Also, two VPAC2 selective antagonists have been described: PG99-465 [140] and VIpep-3 [141]. In terms of non-selective VPAC agonists, there are stearyl-[Nle17]-VIP [142], [R15, 20, 21, L17]-VIP-GRR (IK312532) [143] and [R15, 20, 21, L17]-VIP(1-23) [144]. Besides, *in silico* studies have predicted possible affinity structures for these receptors, constructed classifiers to predict the biological activity of novel VPAC ligands, and highlighted the importance of electrostatic properties in interacting VIP derivatives with receptors [145].

It appears that agonists for treatment should be discussed. After having mentioned the positive and negative effects of VIP and VIP agonists, it would be good to address the potential of VIP as a therapeutic agent for lung diseases. Partial characteristics and treatment of VIP and its analogues are concluded in the following table (Table 3). These analogues, however, consist mainly of the homologous peptide growth hormone-releasing factor (GRF), and binding to other homologous receptors for peptides in the glucagon/VIP/secretin peptide family could affect the interpretations of physiological studies using these two analogues [131]. Unfortunately, when we looked for clinical trials on VIP and its analogues, we found that many approved clinical trials did not have published results. For some published trial results, the original text was unavailable. Searching for clinical trial information on the reagent on the website of the relevant reagent manufacturer also failed.

5. Summary

As a critical physiologically active substance, VIP plays an unignorable role in regulating microenvironmental homeostasis. At the same time, its disorder is also involved in the occurrence and development of various pathophysiological processes. Although VIP is known to have a protective effect in many diseases, such as pulmonary hypertension and asthma, it has been found to promote tumor growth in lung cancer. Diverse approaches have been formulated to optimize VIP efficacy. It is undeniable that VIP and its analogues have therapeutic capabilities and potential as medicines. They have been verified in various animal models, and relevant clinical trials have also been carried out. However, its drug potential and benefits need to be discussed and studied. A comprehensive exploration of its multifaceted involvement in various pathways continues.

Funding

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Table 2
Sequences of VIP and its analogues.

		1				5					10					15					20					25				30		
Natrually occurring peptide																															
VIP		H	S	D	A	V	F	T	D	N	Y	T	R	L	R	K	Q	M	A	V	K	K	Y	L	N	S	I	L	N			
VPAC1 selective agonists																															
[Ala11, 22, 28]-VIP		H	S	D	A	V	F	T	D	N	Y	**A**	R	L	R	K	Q	M	A	V	K	K	**A**	L	N	S	I	L	**A**			
[K15, R16, L27]-VIP(1-7)/GRF(8-27)		H	S	D	A	V	F	T	**N**	**S**	Y	**R**	**K**	**V**	**L**	K	**R**	**L**	**S**	**A**	**R**	K	**L**	L	**Q**	**D**	I	L	N			
GRF-6		H	**a**	D	A	**I**	F	T	**Aib**	**A**	Y	**R**	**K**	**V**	**L**	**A**	**A**	**L**	**Aib**	**A**	**R**	K	**A**	L	**A**	**A**	**A**	**Gab**				
[R16]-chicken Secretin		H	S	D	**G**	**L**	F	T	**S**	**E**	Y	**S**	**K**	**M**	R	**G**	**R**	**A**	**Q**	V	**Q**	K	**F**	**I**	**Q**	**N**	**L**	**M**				
[Tyr(9),Dip(18)]VIP(1-28)		H	S	D	A	V	F	T	D	**Y**	Y	T	R	L	R	K	Q	M	**Dip**	V	K	K	Y	L	N	S	I	L	N			
[Ala(2,8,9,11,19,22,24,25,27,28)]-VIP		H	**A**	D	A	V	F	T	**A**	**A**	Y	**A**	R	L	R	K	Q	M	A	**A**	K	K	**A**	L	**A**	**A**	I	**A**	**A**			
[Ala(2,8,9,11,19,24-28)]-VIP		H	**A**	D	A	V	F	T	**A**	**A**	Y	**A**	R	L	R	K	Q	M	A	**A**	K	K	Y	L	**A**	**A**	**A**	**A**	**A**			
LBT-3393		H	S	D	A	V	F	T	D	N	Y	**t**	R	L	R	**k**	Q	**L**	A	**v**	K	K	Y	**I**	N	**A**	I	**I**	N			
VPAC2 selective agonists																															
Ro 25-1553	acetyl-	H	S	D	A	V	F	T	**E**	N	Y	T	**K**	L	R	K	Q	**Nle**	A	**A**	K	**K***	Y	L	N	**D***	**L**	**K**	**K**	**G**	**G**	**T**
Ro 25-1392	acetyl-	H	S	D	A	V	F	T	**E**	N	**mY**	T	**K**	L	R	K	Q	**Nle**	A	**A**	K	**K***	Y	L	N	**D***	**L**	**K**	**K**			
Ro 24-9981	acetyl-	H	S	D	A	V	F	T	D	N	Y	T	**K**	L	R	K	Q	**Nle**	A	**A**	K	**K**	Y	L	N	**A**	**L**	**K**	**K**	**A**	**A**	**A**
RO5024118	acetyl-	H	S	D	A	**CuMeVal**	F	T	**E**	N	Y	T	**K**	L	R	K	Q	**Nle**	A	**A**	K	**K***	Y	L	N	**D***	**L**	**K**	**K**	**G**	**G**	**T**
BAY 55-9837		H	S	D	A	V	F	T	D	N	Y	T	R	L	R	K	Q	**V**	A	**A**	K	K	Y	L	**Q**	S	I	**K**	N	**K**	**R**	**Y**
BAY(Q9Q28C32)PEG43		H	S	D	A	V	F	T	D	**Q**	Y	T	R	L	R	K	Q	**V**	A	**A**	K	K	Y	L	**Q**	S	I	**K**	**Q**	**K**	**R**	**Y**	**C -PEG43kDa**
LBT-3627		H	**x**	D	A	**x**	F	T	**E**	**x**	**y**	T	**K**	L	R	K	**q**	**L**	A	**A**	**z**	K	Y	**x**	N	**D**	**L**	**K**	**k**	**G**	**g**	**T**
Nonselective agonists																															
stearyl-[Nle17]-VIP	stearyl-	H	S	D	A	V	F	T	D	N	Y	T	R	L	R	K	Q	**Nle**	A	V	K	K	Y	L	N	S	I	L	N			
[R15, 20, 21, L17]-VIP-GRR (IK312532)		H	S	D	A	V	F	T	D	N	Y	T	R	L	R	**R**	Q	**L**	A	V	**R**	**R**	Y	L	N	S	I	L	N	G	**R**	**R**
[R15, 20, 21, L17]-VIP(1–23)		H	S	D	A	V	F	T	D	N	Y	T	R	L	R	**R**	Q	**L**	A	V	**R**	**R**	Y	L								

All peptides are amidated at the C terminus. Side-chains of Lys21 and Asp25 in Ro25-1553, Ro25-1392, and RO5024118 form a lactam ring. The ring information of Ro 24-9981 is not available. Aib, α-aminoisobutyric acid; Gab, γ-aminobutyric acid; Dip,β,β-diphenyl-L-alanine; and mY, methoxy-tyrosine. PEG, polyethylene glycol. Lowercase letters indicate that the amino acid is in the D form. Data in blue indicate changed amino acid residues compared to the original VIP peptide chain.

Table 3
The function of analogues of VIP.

Analogues	Function
[Ala11, 22, 28]-VIP	•It inhibits N-formyl-methionyl-leucyl-phenylalanine-induced ROS production in human monocytes [146]
[K15, R16, L27]-VIP(1-7)/GRF(8-27)	• It has a higher affinity for the human VPAC1 receptor than the rat receptor [129] • It is protective in mouse models of some chronic inflammatory disorders such as rheumatoid arthritis [147], Crohn's disease [148], multiple sclerosis [149], and pancreatitis [150]
[R16]-chicken Secretin	•It has a higher affinity for the rat VPAC1 receptor than for the human receptor [129]
GRF-6	•It has a relatively high affinity for the human VPAC1 receptor but not for the human VPAC2 receptor, rat VPAC1 receptor, rat VPAC2 receptor, or rat PAC1 receptor [130]
[Tyr(9),Dip(18)]VIP(1-28)	•The high affinity and selectivity to the rat VPAC1 receptor selectivity toward other homologous receptors with low affinity to VIP is initially preserved [131]
[Ala2,8,9,11,19,22,24,25,27,28] VIP	• It is a fully efficacious agonist at the human VPAC1 receptor • It has enhanced metabolic stability with a 15,600-fold higher selectivity for the hVPAC1 receptor over the hVPAC2 receptor [132]
[Ala2,8,9,11,19,24-28]VIP	• It is a fully efficacious agonist at the human VPAC1 receptor • It has enhanced metabolic stability with a > 1200-fold higher selectivity for the hVPAC1 receptor over the hVPAC2 receptor [132]
LBT-3393	• It is more resistant to protease activities (pepsin, proteinase K, and chymotrypsin) than VIP • In a disease-relevant PD model, VPAC1-selective agonist LBT-3393 yielded neuro-protective responses [139]
Ro 25-1553	• It prevents antigen-induced bronchocon-striction, vasoconstriction, edema forma-tion, and granulocyte accumulation in guinea pigs [151] • It inhibits IL-2 and IL-4 production in mice [152] • It leads to relaxation of the smooth muscle of the isolated human bronchi and pulmonary artery [76] • It causes a clinically relevant bronchodilatory effect in patients with moderate stable asthma [24]
Ro 25-1392	•It is selectively recognized by VPAC2 agonist, with consequent initiation of cAMP and Ca^{2+} signals and down-regulation of VPAC2 [136]
RO5024118	• It is a selective VPAC2 receptor agonist derived *via* chemical modification of an earlier VPAC2 agonist, Ro 25-1553 • It demonstrates increased stability to neutrophil elastase compared with Ro 25-1553 • In human and guinea pig isolated airway preparations, RO5024118 induces bronchodilatory effects comparable with Ro 25-1553 and the long-acting b-agonist salmeterol • In 5-HT-induced bronchoconstriction in guinea pigs, RO5024118 exhibits inhibitory activity with similar efficacy as, and longer duration than, Ro 25-1553 • In a lipopolysaccharide-mouse model, RO5024118 inhibits neutrophil and $CD8^{+}$ cells, and myeloperoxidase levels • In rats, pretreatment with RO5024118 significantly inhibits porcine pancreatic elastase-induced neutrophil accumulation [25]
BAY 55-9837	• It is a potent and highly selective VPAC2 agonist, which increases glucose-induced insulin secretion and enhances glucose disposal [153] • It increases SMN protein levels and moderates disease phenotype in severe spinal muscular atrophy mouse models [154] • It effectively improves RVSP, total pulmonary resistance index, and CI in MCT-induced pulmonary hypertension [62] • It increases neuronal damage and hemorrhagic transformation after stroke in type 2 diabetic rats [155]
BAY(Q9Q28C32)PEG43	• It is an analogue of BAY 55-9837 • It improves liquid stability and retention of VPAC2-selective binding and activation, as well as prolonged glucose-lowering activity *in vivo* [138]
LBT-3627	• It is resistant to protease activities (pepsin, proteinase K, and chymotrypsin), $t_{1/2}$ = 24.33 min • It is an effective immunomodulatory agent in a disease-relevant PD model. Treatment of MPTP-intoxicated mice with LBT-3627 significantly spares dopaminergic neuronal cell bodies, decreases the amount of reactive microgliosis, decreases levels of pro-inflammatory gene expression associated with the inflammatory response in $CD11b^{+}$ microglia populations, downregulates pro-inflammatory cytokine production, and modulated T-cell phenotypes with treatment [139]
[R15, 20, 21, L17]-VIP-GRR (IK312532)	• It is a long-acting VIP derivative. • It is much more stable against enzymatic digestion compared to VIP, and the protective effect of IK312532 was 1.6-fold higher than that of VIP • It has long-acting relaxant activity in the lungs [143]
[R15, 20, 21, L17]-VIP(1-23)	• It is a shortened analogue of VIP • There is no potential to induce chemical conversion following transpeptidation due to the lack of asparaginyl peptide contained in the sequence of VIP and [Arg15, 20, 21, Leu17]-VIP [144]

Project for 2019 college students of Central South University (2022105330305).

Informed consent

Not applicable.

Ethical approval

This article contains no studies with human participants or animals performed by any authors.

CRediT authorship contribution statement

H.L.Z. and Y.Z. conceived the idea and wrote this manuscript. H.L.Z, P.Z.L., and D.L. reviewed this manuscript. C.X.G. and Y.Z. conceived the idea and critically reviewed this manuscript. All authors had final approval of the submitted version.

Declaration of competing interest

The authors declare that they have no conflict of interest.

References

[1] M. Zhou, H. Wang, X. Zeng, et al., Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 394 (10204) (2019) 1145–1158.
[2] H. Li, S.M. Liu, X.H. Yu, et al., Coronavirus disease 2019 (COVID-19): current status and future perspectives, Int. J. Antimicrob. Agents 55 (5) (2020) 105951.
[3] T.W. Moody, B. Nuche-Berenguer, R.T. Jensen, Vasoactive intestinal peptide/pituitary adenylate cyclase activating polypeptide, and their receptors and cancer, Curr. Opin. Endocrinol. Diabetes Obes. 23 (1) (2016) 38–47.
[4] B. Burian, A. Storka, B.A. Marzluf, et al., Vasoactive intestinal peptide (VIP) receptor expression in monocyte-derived macrophages from COPD patients, Peptides 31 (4) (2010) 603–608.
[5] G.O. Barbezat, M.I. Grossman, Intestinal secretion: stimulation by peptides, Science 174 (4007) (1971) 422–424.
[6] S. Onoue, S. Misaka, S. Yamada, Structure-activity relationship of vasoactive intestinal peptide (VIP): potent agonists and potential clinical applications, Naunyn Schmiedeberg's Arch. Pharmacol. 377 (4–6) (2008) 579–590.
[7] D. Wu, D. Lee, Y.K. Sung, Prospect of vasoactive intestinal peptide therapy for COPD/PAH and asthma: a review, Respir. Res. 12 (1) (2011) 45.
[8] D.A. Groneberg, K.F. Rabe, A. Fischer, Novel concepts of neuropeptide-based drug therapy: vasoactive intestinal polypeptide and its receptors, Eur. J. Pharmacol. 533 (1–3) (2006) 182–194.
[9] I. Virgolini, A. Kurtaran, M. Raderer, et al., Vasoactive intestinal peptide receptor scintigraphy, J. Nucl. Med. 36 (10) (1995) 1732–1739.
[10] T.W. Moody, I. Ramos-Alvarez, R.T. Jensen, Neuropeptide G protein-coupled receptors as oncotargets, Front. Endocrinol. 9 (2018) 345.
[11] F. Merech, E. Soczewski, V. Hauk, et al., Vasoactive intestinal peptide induces glucose and neutral amino acid uptake through mTOR signalling in human cytotrophoblast cells, Sci. Rep. 9 (1) (2019) 17152.
[12] J. Wang, Y.X. Shang, X.X. Cai, et al., Vasoactive intestinal peptide inhibits airway smooth muscle cell proliferation in a mouse model of asthma via the ERK1/2 signaling pathway, Exp. Cell Res. 364 (2) (2018) 168–174.
[13] M. Delgado, Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit the MEKK1/MEK4/JNK signaling pathway in endotoxin-activated microglia, Biochem. Biophys. Res. Commun. 293 (2) (2002) 771–776.
[14] L. Shi, L. Feng, M.L. Zhu, et al., Vasoactive intestinal peptide stimulates bone marrow-mesenchymal stem cells osteogenesis differentiation by activating Wnt/β-catenin signaling pathway and promotes rat skull defect repair, Stem Cells Dev. 29 (10) (2020) 655–666.
[15] G.S. Filippatos, N. Gangopadhyay, O. Lalude, et al., Regulation of apoptosis by vasoactive peptides, Am. J. Phys. Lung Cell. Mol. Phys. 281 (4) (2001) L749–L761.
[16] S.I. Said, The vasoactive intestinal peptide gene is a key modulator of pulmonary vascular remodeling and inflammation, Ann. N. Y. Acad. Sci. 1144 (2008) 148–153.
[17] J. Leceta, R.P. Gomariz, C. Martinez, et al., Receptors and transcriptional factors involved in the anti-inflammatory activity of VIP and PACAP, Ann. N. Y. Acad. Sci. 921 (2000) 92–102.
[18] Y. Zhou, C.Y. Zhang, J.X. Duan, et al., Vasoactive intestinal peptide suppresses the NLRP3 inflammasome activation in lipopolysaccharide-induced acute lung injury mice and macrophages, Biomed. Pharmacother. 121 (2020) 109596.
[19] M. Delgado, E.J. Munoz-Elias, Y. Kan, et al., Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit tumor necrosis factor alpha transcriptional activation by regulating nuclear factor-kB and cAMP response element-binding protein/c-Jun, J. Biol. Chem. 273 (47) (1998) 31427–31436.
[20] A.M. Szema, S.A. Hamidi, S. Lyubsky, et al., Mice lacking the VIP gene show airway hyperresponsiveness and airway inflammation, partially reversible by VIP, Am. J. Phys. Lung Cell. Mol. Phys. 291 (5) (2006) L880–L886.
[21] S. Onoue, S. Misaka, Y. Aoki, et al., Inhalable powder formulation of vasoactive intestinal peptide derivative, [R15,20,21, L17]-VIP-GRR, attenuated neutrophilic airway inflammation in cigarette smoke-exposed rats, Eur. J. Pharm. Sci. 41 (3–4) (2010) 508–514.
[22] T. Saga, S.I. Said, Vasoactive intestinal peptide relaxes isolated strips of human bronchus, pulmonary artery, and lung parenchyma, Trans. Assoc. Am. Phys. 97 (1984) 304–310.
[23] J.B. Palmer, F.M. Cuss, P.J. Barnes, VIP and PHM and their role in nonadrenergic inhibitory responses in isolated human airways, J. Appl. Physiol. (1985) 61 (4) (1986) 1322–1328.
[24] A. Lindén, L. Hansson, A. Andersson, et al., Bronchodilation by an inhaled VPAC (2) receptor agonist in patients with stable asthma, Thorax 58 (3) (2003) 217–221.
[25] S.A. Tannu, L.M. Renzetti, N. Tare, et al., Dual bronchodilatory and pulmonary anti-inflammatory activity of RO5024118, a novel agonist at vasoactive intestinal peptide VPAC2 receptors, Br. J. Pharmacol. 161 (6) (2010) 1329–1342.
[26] S.I. Said, V. Mutt, Polypeptide with broad biological activity: isolation from small intestine, Science 169 (3951) (1970) 1217–1218.
[27] R.J. Altiere, L. Diamond, Relaxation of cat tracheobronchial and pulmonary arterial smooth muscle by vasoactive intestinal peptide: lack of influence by peptidase inhibitors, Br. J. Pharmacol. 82 (2) (1984) 321–328.
[28] M. Huang, H. Shirahase, O.P. Rorstad, Comparative study of vascular relaxation and receptor binding by PACAP and VIP, Peptides 14 (4) (1993) 755–762.
[29] R.D. Dey, W.A. Shannon Jr., S.I. Said, Localization of VIP-immunoreactive nerves in airways and pulmonary vessels of dogs, cat, and human subjects, Cell Tissue Res. 220 (2) (1981) 231–238.
[30] S.T. Ballard, D. Spadafora, Fluid secretion by submucosal glands of the tracheobronchial airways, Respir. Physiol. Neurobiol. 159 (3) (2007) 271–277.
[31] D.A. Groneberg, P. Hartmann, Q.T. Dinh, et al., Expression and distribution of vasoactive intestinal polypeptide receptor VPAC(2) mRNA in human airways, Lab. Investig. 81 (5) (2001) 749–755.
[32] J.H. Jeong, N.S. Joo, P.H. Hwang, et al., Mucociliary clearance and submucosal gland secretion in the ex vivo ferret trachea, Am. J. Phys. Lung Cell. Mol. Phys. 307 (1) (2014) L83–L93.
[33] D.B. McMahon, R.M. Carey, M.A. Kohanski, et al., Neuropeptide regulation of secretion and inflammation in human airway gland serous cells, Eur. Respir. J. (2020) 55(4).
[34] D. Ganea, K.M. Hooper, W. Kong, The neuropeptide vasoactive intestinal peptide: direct effects on immune cells and involvement in inflammatory and autoimmune diseases, Acta Physiol (Oxford) 213 (2) (2015) 442–452.
[35] J. Voice, S. Donnelly, G. Dorsam, et al., c-Maf and JunB mediation of Th2 differentiation induced by the type 2 G protein-coupled receptor (VPAC2) for vasoactive intestinal peptide, J. Immunol. 172 (12) (2004) 7289–7296.
[36] X. Song, S. Pi, Y. Gao, et al., The role of vasoactive intestinal peptide and mast cells in the regulatory effect of Lactobacillus casei ATCC 393 on intestinal mucosal immune barrier, Front. Immunol. 12 (2021) 723173.
[37] D.E. Paparini, R.H. Choudhury, D.M. Vota, et al., Vasoactive intestinal peptide shapes first-trimester placenta trophoblast, vascular, and immune cell cooperation, Br. J. Pharmacol. 176 (7) (2019) 964–980.
[38] Y. He, C. Li, Z. Wang, et al., C-fiber degeneration enhances alveolar macrophage-mediated IFN-α/β response to respiratory syncytial virus, Microbiol Spectr. 10 (6) (2022), e0241022.
[39] A. Fraser, G. Evan, A license to kill, Cell 85 (6) (1996) 781–784.
[40] S.I. Said, K.G. Dickman, Pathways of inflammation and cell death in the lung: modulation by vasoactive intestinal peptide, Regul. Pept. 93 (1–3) (2000) 21–29.
[41] S. Misaka, H. Sato, Y. Aoki, et al., Novel vasoactive intestinal peptide derivatives with improved stability protect rat alveolar L2 cells from cigarette smoke-induced cytotoxicity and apoptosis, Peptides 32 (2) (2011) 401–407.
[42] T.W. Moody, I. Gozes, Vasoactive intestinal peptide receptors: a molecular target in breast and lung cancer, Curr. Pharm. Des. 13 (11) (2007) 1099–1104.
[43] A.M. Szema, S.A. Hamidi, A. Koller, et al., Vasoactive Intestinal Peptide Knockout (VIP KO) mouse model of sulfite-sensitive asthma: up-regulation of novel lung carbonyl reductase, BMC Immunol. 12 (2011) 66.
[44] L. Li, H. She, S. Yue, et al., Vasoactive intestinal peptide induces surfactant protein A expression in ATII cells through activation of PKC/c-Fos pathway, Peptides 31 (11) (2010) 2046–2051.
[45] L. Li, Z.Q. Luo, F.W. Zhou, et al., Effect of vasoactive intestinal peptide on pulmonary surfactants phospholipid synthesis in lung explants, Acta Pharmacol. Sin. 25 (12) (2004) 1652–1658.
[46] C.X. Guan, Y.R. Cui, G.Y. Sun, et al., Role of CREB in vasoactive intestinal peptide-mediated wound healing in human bronchial epithelial cells, Regul. Pept. 153 (1–3) (2009) 64–69.
[47] C.X. Guan, Y.R. Cui, M. Zhang, et al., Intracellular signaling molecules involved in vasoactive intestinal peptide-mediated wound healing in human bronchial epithelial cells, Peptides 28 (9) (2007) 1667–1673.
[48] C.X. Guan, M. Zhang, X.Q. Qin, et al., Vasoactive intestinal peptide enhances wound healing and proliferation of human bronchial epithelial cells, Peptides 27 (12) (2006) 3107–3114.
[49] T. Klouda, K. Yuan, Inflammation in pulmonary arterial hypertension, Adv. Exp. Med. Biol. 1303 (2021) 351–372.
[50] N.F. Ruopp, B.A. Cockrill, Diagnosis and treatment of pulmonary arterial hypertension: a review, Jama 327 (14) (2022) 1379–1391.
[51] L.J. Rubin, J. Mendoza, M. Hood, et al., Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial, Ann. Intern. Med. 112 (7) (1990) 485–491.
[52] N. Galiè, Do we need controlled clinical trials in pulmonary arterial hypertension? Eur. Respir. J. 17 (1) (2001) 1–3.
[53] C.J. Rhodes, A. Davidson, J.S. Gibbs, et al., Therapeutic targets in pulmonary arterial hypertension, Pharmacol. Ther. 121 (1) (2009) 69–88.
[54] R.L. Benza, M. Gomberg-Maitland, T. Demarco, et al., Endothelin-1 pathway polymorphisms and outcomes in pulmonary arterial hypertension, Am. J. Respir. Crit. Care Med. 192 (11) (2015) 1345–1354.
[55] M.A. de Raaf, M. Beekhuijzen, C. Guignabert, et al., Endothelin-1 receptor antagonists in fetal development and pulmonary arterial hypertension, Reprod. Toxicol. 56 (2015) 45–51.
[56] J. Wharton, J.W. Strange, G.M. Møller, et al., Antiproliferative effects of phosphodiesterase type 5 inhibition in human pulmonary artery cells, Am. J. Respir. Crit. Care Med. 172 (1) (2005) 105–113.
[57] R.T. Schermuly, S.S. Pullamsetti, G. Kwapiszewska, et al., Phosphodiesterase 1 upregulation in pulmonary arterial hypertension: target for reverse-remodeling therapy, Circulation 115 (17) (2007) 2331–2339.
[58] S.A. Hamidi, R.Z. Lin, A.M. Szema, et al., VIP and endothelin receptor antagonist: an effective combination against experimental pulmonary arterial hypertension, Respir. Res. 12 (1) (2011) 141.
[59] S.I. Said, S.A. Hamidi, K.G. Dickman, et al., Moderate pulmonary arterial hypertension in male mice lacking the vasoactive intestinal peptide gene, Circulation 115 (10) (2007) 1260–1268.
[60] W. Habre, G. Albu, T.Z. Janosi, et al., Prevention of bronchial hyperreactivity in a rat model of precapillary pulmonary hypertension, Respir. Res. 12 (1) (2011) 58.

[61] A. Vuckovic, B. Rondelet, J.P. Brion, et al., Expression of vasoactive intestinal peptide and related receptors in overcirculation-induced pulmonary hypertension in piglets, Pediatr. Res. 66 (4) (2009) 395–399.
[62] M. Koga, Y. Mizuno, I. Watanabe, et al., Role of VPAC2 receptor in monocrotaline-induced pulmonary hypertension in rats, J. Appl. Physiol. (1985) 117 (4) (2014) 383–391.
[63] R.C. St Hilaire, P.J. Kadowitz, J.R. Jeter Jr., Adenoviral transfer of vasoactive intestinal peptide (VIP) gene inhibits rat aortic and pulmonary artery smooth muscle cell proliferation, Peptides 30 (12) (2009) 2323–2329.
[64] R.C. St Hilaire, S.N. Murthy, P.J. Kadowitz, et al., Role of VPAC1 and VPAC2 in VIP mediated inhibition of rat pulmonary artery and aortic smooth muscle cell proliferation, Peptides 31 (8) (2010) 1517–1522.
[65] R. Zolty, Pulmonary arterial hypertension specific therapy: the old and the new, Pharmacol. Ther. 214 (2020) 107576.
[66] H.H. Leuchte, C. Baezner, R.A. Baumgartner, et al., Inhalation of vasoactive intestinal peptide in pulmonary hypertension, Eur. Respir. J. 32 (5) (2008) 1289–1294.
[67] V. Petkov, W. Mosgoeller, R. Ziesche, et al., Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension, J. Clin. Invest. 111 (9) (2003) 1339–1346.
[68] I. Haberl, K. Frei, R. Ramsebner, et al., Vasoactive intestinal peptide gene alterations in patients with idiopathic pulmonary arterial hypertension, Eur. J. Hum. Genet. 15 (1) (2007) 18–22.
[69] K.K. Stone, E. Bermúdez, W.A. Pryor, Aqueous extracts of cigarette tar containing the tar free radical cause DNA nicks in mammalian cells, Environ. Health Perspect. 102 Suppl 10 (Suppl. 10) (1994) 173–178.
[70] S. Onoue, S. Yamada, T. Yajima, Bioactive analogues and drug delivery systems of vasoactive intestinal peptide (VIP) for the treatment of asthma/COPD, Peptides 28 (9) (2007) 1640–1650.
[71] J. Cai, Q. Chen, E. Mehrabi Nasab, et al., Immunomodulatory effect of N-acetyl-seryl-aspartyl-proline and vasoactive intestinal peptide on chronic obstructive pulmonary disease pathophysiology, Fundam. Clin. Pharmacol. 36 (6) (2022) 1005–1010.
[72] S. Misaka, Y. Aoki, S. Karaki, et al., Inhalable powder formulation of a stabilized vasoactive intestinal peptide (VIP) derivative: anti-inflammatory effect in experimental asthmatic rats, Peptides 31 (1) (2010) 72–78.
[73] A.K. Verma, M. Manohar, S. Upparahalli Venkateshaiah, et al., Neuroendocrine cells derived chemokine vasoactive intestinal polypeptide (VIP) in allergic diseases, Cytokine Growth Factor Rev. 38 (2017) 37–48.
[74] J. Mandal, M. Roth, L. Costa, et al., Vasoactive intestinal peptide for diagnosing exacerbation in chronic obstructive pulmonary disease, Respiration 90 (5) (2015) 357–368.
[75] D. Miotto, P. Boschetto, I. Bononi, et al., Vasoactive intestinal peptide receptors in the airways of smokers with chronic bronchitis, Eur. Respir. J. 24 (6) (2004) 958–963.
[76] D.T. Schmidt, E. Rühlmann, B. Waldeck, et al., The effect of the vasoactive intestinal polypeptide agonist Ro 25-1553 on induced tone in isolated human airways and pulmonary artery, Naunyn Schmiedeberg's Arch. Pharmacol. 364 (4) (2001) 314–320.
[77] A.M. Szema, E. Forsyth, B. Ying, et al., NFATc3 and VIP in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease, PLoS One 12 (1) (2017), e0170606.
[78] A. Papi, C. Brightling, S.E. Pedersen, et al., Asthma, Lancet 391 (10122) (2018) 783–800.
[79] S.I. Said, S.A. Hamidi, Bosc L. Gonzalez, Asthma and pulmonary arterial hypertension: do they share a key mechanism of pathogenesis? Eur. Respir. J. 35 (4) (2010) 730–734.
[80] S.S. Athari, Z. Pourpak, G. Folkerts, et al., Conjugated alpha-alumina nanoparticle with vasoactive intestinal peptide as a nano-drug in treatment of allergic asthma in mice, Eur. J. Pharmacol. 791 (2016) 811–820.
[81] A.E. Samarasinghe, S.A. Hoselton, J.M. Schuh, The absence of VPAC2 leads to aberrant antibody production in Aspergillus fumigatus sensitized and challenged mice, Peptides 32 (1) (2011) 131–137.
[82] S.I. Said, Vasoactive intestinal polypeptide and asthma, N. Engl. J. Med. 320 (19) (1989) 1271–1273.
[83] A.H. Morice, P.S. Sever, Vasoactive intestinal peptide as a bronchodilator in severe asthma, Peptides 7 (Suppl. 1) (1986) 279–280.
[84] A. Morice, R.J. Unwin, P.S. Sever, Vasoactive intestinal peptide causes bronchodilatation and protects against histamine-induced bronchoconstriction in asthmatic subjects, Lancet 2 (8361) (1983) 1225–1227.
[85] A. Morice, R. Unwin, P. Sever, VIP as bronchodilator, Lancet 1 (8374) (1984) 457–458.
[86] T.M. Endres, M.W. Konstan, What is cystic fibrosis? Jama 327 (2) (2022) 191.
[87] L. Cuthbertson, A.W. Walker, A.E. Oliver, et al., Lung function and microbiota diversity in cystic fibrosis, Microbiome 8 (1) (2020) 45.
[88] S.C. Ranganathan, G.L. Hall, P.D. Sly, et al., Early lung disease in infants and preschool children with cystic fibrosis. What have we learned and what should we do about it? Am. J. Respir. Crit. Care Med. 195 (12) (2017) 1567–1575.
[89] M. Shteinberg, I.J. Haq, D. Polineni, et al., Cystic fibrosis, Lancet 397 (10290) (2021) 2195–2211.
[90] N.S. Joo, T. Irokawa, J.V. Wu, et al., Absent secretion to vasoactive intestinal peptide in cystic fibrosis airway glands, J. Biol. Chem. 277 (52) (2002) 50710–50715.
[91] A. Semaniakou, S. Brothers, G. Gould, et al., Disrupted local innervation results in less VIP expression in CF mice tissues, J. Cyst. Fibros. 20 (1) (2021) 154–164.
[92] N. Alcolado, D.J. Conrad, S. Rafferty, et al., VIP-dependent increase in F508del-CFTR membrane localization is mediated by PKCε, Am. J. Phys. Cell Phys. 301 (1) (2011) C53–C65.
[93] A. Abu-Arish, E. Pandžić, D. Kim, et al., Agonists that stimulate secretion promote the recruitment of CFTR into membrane lipid microdomains, J. Gen. Physiol. 151 (6) (2019) 834–849.
[94] N.G. Alcolado, D.J. Conrad, D. Poroca, et al., Cystic fibrosis transmembrane conductance regulator dysfunction in VIP knockout mice, Am. J. Phys. Cell Phys. 307 (2) (2014) C195–C207.
[95] J.Y. Choi, N.S. Joo, M.E. Krouse, et al., Synergistic airway gland mucus secretion in response to vasoactive intestinal peptide and carbachol is lost in cystic fibrosis, J. Clin. Invest. 117 (10) (2007) 3118–3127.
[96] Y.Q. He, C.C. Zhou, L.Y. Yu, et al., Natural product derived phytochemicals in managing acute lung injury by multiple mechanisms, Pharmacol. Res. 163 (2021) 105224.
[97] Z. Yan, Z. Xiaoyu, S. Zhixin, et al., Rapamycin attenuates acute lung injury induced by LPS through inhibition of Th17 cell proliferation in mice, Sci. Rep. 6 (2016) 20156.
[98] W.Z. Ran, L. Dong, C.Y. Tang, et al., Vasoactive intestinal peptide suppresses macrophage-mediated inflammation by downregulating interleukin-17A expression via PKA- and PKC-dependent pathways, Int. J. Exp. Pathol. 96 (4) (2015) 269–275.
[99] G.Y. Sun, H.H. Yang, X.X. Guan, et al., Vasoactive intestinal peptide overexpression mediated by lentivirus attenuates lipopolysaccharide-induced acute lung injury in mice by inhibiting inflammation, Mol. Immunol. 97 (2018) 8–15.
[100] G.Y. Sun, C.X. Guan, Y. Zhou, et al., Vasoactive intestinal peptide re-balances TREM-1/TREM-2 ratio in acute lung injury, Regul. Pept. 167 (1) (2011) 56–64.
[101] Y.F. Zhang, J. Zhang, C.C. Sun, et al., Vasoactive intestinal peptide inhibits the activation of murine fibroblasts and expression of interleukin 17 receptor C, Cell Biol. Int. 43 (7) (2019) 770–780.
[102] S.A. Hamidi, K.G. Dickman, H. Berisha, et al., 17β-estradiol protects the lung against acute injury: possible mediation by vasoactive intestinal polypeptide, Endocrinology 152 (12) (2011) 4729–4737.
[103] J.J. Grailer, B.A. Canning, M. Kalbitz, et al., Critical role for the NLRP3 inflammasome during acute lung injury, J. Immunol. 192 (12) (2014) 5974–5983.
[104] J.R. Temerozo, C.Q. Sacramento, N. Fintelman-Rodrigues, et al., VIP plasma levels associate with survival in severe COVID-19 patients, correlating with protective effects in SARS-CoV-2-infected cells, J. Leukoc. Biol. 111 (5) (2022) 1107–1121.
[105] T. Mukherjee, T. Behl, S. Sharma, et al., Anticipated pharmacological role of Aviptadil on COVID-19, Environ. Sci. Pollut. Res. Int. 29 (6) (2022) 8109–8125.
[106] M. Boesing, K. Abig, M. Brändle, et al., Inhaled aviptadil for the possible treatment of COVID-19 in patients at high risk for ARDS: study protocol for a randomized, placebo-controlled, and multicenter trial, Trials 23 (1) (2022) 790.
[107] J.G. Youssef, P. Lavin, D.A. Schoenfeld, et al., The use of IV vasoactive intestinal peptide (aviptadil) in patients with critical COVID-19 respiratory failure: results of a 60-day randomized controlled trial, Crit. Care Med. 50 (11) (2022) 1545–1554.
[108] L. Richeldi, H.R. Collard, M.G. Jones, Idiopathic pulmonary fibrosis, Lancet 389 (10082) (2017) 1941–1952.
[109] G. Sgalla, B. Iovene, M. Calvello, et al., Idiopathic pulmonary fibrosis: pathogenesis and management, Respir. Res. 19 (1) (2018) 32.
[110] J.X. Duan, X.X. Guan, H.H. Yang, et al., Vasoactive intestinal peptide attenuates bleomycin-induced murine pulmonary fibrosis by inhibiting epithelial-mesenchymal transition: restoring autophagy in alveolar epithelial cells, Int. Immunopharmacol. 101 (Pt B) (2021), 108211.
[111] A.A. Thai, B.J. Solomon, L.V. Sequist, et al., Lung cancer, Lancet 398 (10299) (2021) 535–554.
[112] K. Maruno, A. Absood, S.I. Said, Vasoactive intestinal peptide inhibits human small-cell lung cancer proliferation in vitro and in vivo, Proc. Natl. Acad. Sci. U. S. A. 95 (24) (1998) 14373–14378.
[113] M. Casibang, S. Purdom, S. Jakowlew, et al., Prostaglandin E2 and vasoactive intestinal peptide increase vascular endothelial cell growth factor mRNAs in lung cancer cells, Lung Cancer 31 (2–3) (2001) 203–212.
[114] T.W. Moody, J. Walters, M. Casibang, et al., VPAC1 receptors and lung cancer, Ann. N. Y. Acad. Sci. 921 (2000) 26–32.
[115] A.G. D'Amico, G. Maugeri, D.M. Rasà, et al., Modulatory role of PACAP and VIP on HIFs expression in lung adenocarcinoma, Peptides 146 (2021) 170672.
[116] E. Gelber, R. Granoth, M. Fridkin, et al., A lipophilic vasoactive intestinal peptide analog enhances the antiproliferative effect of chemotherapeutic agents on cancer cell lines, Cancer 92 (8) (2001) 2172–2180.
[117] C.R. Sears, T. Peikert, J.D. Possick, et al., Knowledge gaps and research priorities in immune checkpoint inhibitor-related pneumonitis. An official American Thoracic Society research statement, Am. J. Respir. Crit. Care Med. 200 (6) (2019) e31–e43.
[118] B.C. Frye, F. Meiss, D. von Bubnoff, et al., Vasoactive intestinal peptide in checkpoint inhibitor-induced pneumonitis, N. Engl. J. Med. 382 (26) (2020) 2573–2574.
[119] T.W. Moody, P. Moreno, R.T. Jensen, Neuropeptides as lung cancer growth factors, Peptides 72 (2015) 106–111.
[120] T.W. Moody, F. Zia, M. Draoui, et al., A vasoactive intestinal peptide antagonist inhibits non-small cell lung cancer growth, Proc. Natl. Acad. Sci. U. S. A. 90 (10) (1993) 4345–4349.

[121] I. Virgolini, M. Raderer, A. Kurtaran, et al., Vasoactive intestinal peptide-receptor imaging for the localization of intestinal adenocarcinomas and endocrine tumors, N. Engl. J. Med. 331 (17) (1994) 1116–1121.
[122] S. Domschke, W. Domschke, S.R. Bloom, et al., Vasoactive intestinal peptide in man: pharmacokinetics, metabolic and circulatory effects, Gut 19 (11) (1978) 1049–1053.
[123] P.G. Burhol, I. Lygren, H.L. Waldum, Radioimmunoassay of vasoactive intestinal polypeptide in plasma, Scand. J. Gastroenterol. 13 (7) (1978) 807–813.
[124] R.J. Henning, D.R. Sawmiller, Vasoactive intestinal peptide: cardiovascular effects, Cardiovasc. Res. 49 (1) (2001) 27–37.
[125] W.E. Berger, Paediatric pulmonary drug delivery: considerations in asthma treatment, Expert Opin. Drug Deliv. 2 (6) (2005) 965–980.
[126] Y. Ohmori, S. Onoue, K. Endo, et al., Development of dry powder inhalation system of novel vasoactive intestinal peptide (VIP) analogue for pulmonary administration, Life Sci. 79 (2) (2006) 138–143.
[127] P. Nicole, L. Lins, C. Rouyer-Fessard, et al., Identification of key residues for interaction of vasoactive intestinal peptide with human VPAC1 and VPAC2 receptors and development of a highly selective VPAC1 receptor agonist. Alanine scanning and molecular modeling of the peptide, J. Biol. Chem. 275 (31) (2000) 24003–24012.
[128] P. Robberecht, P. De Neef, R.A. Lefebvre, Influence of selective VIP receptor agonists in the rat gastric fundus, Eur. J. Pharmacol. 359 (1) (1998) 77–80.
[129] P. Gourlet, A. Vandermeers, P. Vertongen, et al., Development of high affinity selective VIP1 receptor agonists, Peptides 18 (10) (1997) 1539–1545.
[130] T. Ito, H. Igarashi, T.K. Pradhan, et al., GI side-effects of a possible therapeutic GRF analogue in monkeys are likely due to VIP receptor agonist activity, Peptides 22 (7) (2001) 1139–1151.
[131] J.W. Tams, R.M. Jorgensen, A. Holm, et al., Creation of a selective antagonist and agonist of the rat VPAC(1) receptor using a combinatorial approach with vasoactive intestinal peptide 6-23 as template, Mol. Pharmacol. 58 (5) (2000) 1035–1041.
[132] H. Igarashi, T. Ito, S.A. Mantey, et al., Development of simplified vasoactive intestinal peptide analogs with receptor selectivity and stability for human vasoactive intestinal peptide/pituitary adenylate cyclase-activating polypeptide receptors, J. Pharmacol. Exp. Ther. 315 (1) (2005) 370–381.
[133] P. Gourlet, M.C. Vandermeers-Piret, J. Rathé, et al., Vasoactive intestinal peptide modification at position 22 allows discrimination between receptor subtypes, Eur. J. Pharmacol. 348 (1) (1998) 95–99.
[134] P. Gourlet, P. De Neef, J. Cnudde, et al., In vitro properties of a high affinity selective antagonist of the VIP1 receptor, Peptides 18 (10) (1997) 1555–1560.
[135] D.R. Bolin, J. Michalewsky, M.A. Wasserman, et al., Design and development of a vasoactive intestinal peptide analog as a novel therapeutic for bronchial asthma, Biopolymers 37 (2) (1995) 57–66.
[136] M. Xia, S.P. Sreedharan, D.R. Bolin, et al., Novel cyclic peptide agonist of high potency and selectivity for the type II vasoactive intestinal peptide receptor, J. Pharmacol. Exp. Ther. 281 (2) (1997) 629–633.
[137] X.P. Gao, I. Rubinstein, The stable VIP analogue, Ro 24-9981, potentiates bradykinin-induced increases in clearance of macromolecules, Am. J. Phys. 269 (5 Pt 2) (1995) H1648–H1655.
[138] C.Q. Pan, F. Li, I. Tom, et al., Engineering novel VPAC2-selective agonists with improved stability and glucose-lowering activity in vivo, J. Pharmacol. Exp. Ther. 320 (2) (2007) 900–906.
[139] K.E. Olson, L.M. Kosloski-Bilek, K.M. Anderson, et al., Selective VIP receptor agonists facilitate immune transformation for dopaminergic neuroprotection in MPTP-intoxicated mice, J. Neurosci. 35 (50) (2015) 16463–16478.
[140] D. Moreno, P. Gourlet, P. De Neef, et al., Development of selective agonists and antagonists for the human vasoactive intestinal polypeptide VPAC(2) receptor, Peptides 21 (10) (2000) 1543–1549.
[141] K. Sakamoto, R. Koyama, Y. Kamada, et al., Discovery of artificial VIPR2-antagonist peptides possessing receptor- and ligand-selectivity, Biochem. Biophys. Res. Commun. 503 (3) (2018) 1973–1979.
[142] I. Gozes, G. Lilling, R. Glazer, et al., Superactive lipophilic peptides discriminate multiple vasoactive intestinal peptide receptors, J. Pharmacol. Exp. Ther. 273 (1) (1995) 161–167.
[143] S. Onoue, K. Endo, Y. Ohmori, et al., Long-acting analogue of vasoactive intestinal peptide, [R15, 20, 21, L17]-VIP-GRR (IK312532), protects rat alveolar L2 cells from the cytotoxicity of cigarette smoke, Regul. Pept. 123 (1–3) (2004) 193–199.
[144] S. Onoue, Y. Ohmori, A. Matsumoto, et al., Structure-activity relationship of synthetic truncated analogues of vasoactive intestinal peptide (VIP): an enhancement in the activity by a substitution with arginine, Life Sci. 74 (12) (2004) 1465–1477.
[145] J. Li, X. Wang, H. Liu, et al., In silico classification and prediction of VIP derivatives as VPAC1/VPAC2 receptor agonists/antagonists, Comb. Chem. High Throughput Screen. 18 (1) (2015) 33–41.
[146] P. Chedid, T. Boussetta, P.M. Dang, et al., Vasoactive intestinal peptide dampens formyl-peptide-induced ROS production and inflammation by targeting a MAPK-p47(phox) phosphorylation pathway in monocytes, Mucosal Immunol. 10 (2) (2017) 332–340.
[147] G.S. Firestein, VIP: a very important protein in arthritis, Nat. Med. 7 (5) (2001) 537–538.
[148] C. Abad, C. Martinez, M.G. Juarranz, et al., Therapeutic effects of vasoactive intestinal peptide in the trinitrobenzene sulfonic acid mice model of Crohn's disease, Gastroenterology 124 (4) (2003) 961–971.
[149] E. Gonzalez-Rey, A. Fernandez-Martin, A. Chorny, et al., Therapeutic effect of vasoactive intestinal peptide on experimental autoimmune encephalomyelitis: down-regulation of inflammatory and autoimmune responses, Am. J. Pathol. 168 (4) (2006) 1179–1188.
[150] M. Kojima, T. Ito, T. Oono, et al., VIP attenuation of the severity of experimental pancreatitis is due to VPAC1 receptor-mediated inhibition of cytokine production, Pancreas 30 (1) (2005) 62–70.
[151] M. O'Donnell, R.J. Garippa, N. Rinaldi, et al., Ro 25-1553: a novel, long-acting vasoactive intestinal peptide agonist. Part I: in vitro and in vivo bronchodilator studies, J. Pharmacol. Exp. Ther. 270 (3) (1994) 1282–1288.
[152] H. Tang, A. Welton, D. Ganea, Neuropeptide regulation of cytokine expression: effects of VIP and Ro 25-1553, J. Interf. Cytokine Res. 15 (11) (1995) 993–1003.
[153] M. Tsutsumi, T.H. Claus, Y. Liang, et al., A potent and highly selective VPAC2 agonist enhances glucose-induced insulin release and glucose disposal: a potential therapy for type 2 diabetes, Diabetes 51 (5) (2002) 1453–1460.
[154] J. Hadwen, D. MacKenzie, F. Shamim, et al., VPAC2 receptor agonist BAY 55-9837 increases SMN protein levels and moderates disease phenotype in severe spinal muscular atrophy mouse models, Orphanet J. Rare Dis. 9 (2014) 4.
[155] V. Darsalia, S. Mansouri, P. Wolbert, et al., The specific VPAC2 agonist Bay 55-9837 increases neuronal damage and hemorrhagic transformation after stroke in type 2 diabetic rats, Neuropeptides 47 (2) (2013) 133–137.